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WO 01/40243 A2

(54) Title: PARTIAL OR FULL A₁ AGONISTS - N⁶ HETEROCYCLIC 5'-THIO SUBSTITUTED ADENOSINE DERIVATIVES

(57) Abstract: N⁶ heterocyclic 5' modified adenosine derivatives that are adenosine A₁ receptor partial or full agonists, and as such, are useful for modifying cardiac activity, modifying adipocyte function, treating central nervous system disorders, and treating diabetic disorders and obesity in mammals, and especially in humans.

WO 01/40243

PCT/US00/42509

5 **TITLE:** **PARTIAL OR FULL A₁ AGONISTS - N⁶ HETEROCYCLIC 5'-THIO SUBSTITUTED ADENOSINE DERIVATIVES**

BACKGROUND OF THE INVENTION

10 **(1) Field of the Invention**

 This invention includes stable and useful drugs and pro-drugs that are N⁶ heterocyclic 5'-thio modified adenosine derivatives. The compositions of this invention are selective, partial or full adenosine A₁ receptor agonists, and as such, are useful for modifying cardiac activity, modifying adipocyte function, treating central nervous system disorders, and treating
15 diabetic disorders and obesity in mammals, and especially in humans.

(2) Description of the Art

 There are at least two subtypes of adenosine receptors in the heart: A₁ and A_{2A}. Each subtype affects different physiological functions. The A₁ adenosine receptor mediates two distinct physiological responses. Inhibition of the cardiostimulatory effects of catecholamine
20 are mediated via the inhibition of adenylate cyclase, whereas the direct effects to slow the heart rate (HR) and to prolong impulse propagation through the AV node are due in great part to activation of I_{KAdo}. (B. Lerman and L. Belardinelli Circulation, Vol. 83 (1991), P 1499-1509 and J. C. Shryock and L. Belardinelli The Am. J. Cardiology, Vol. 79 (1997) P 2-10). Both, the anti-β-adrenergic action and direct depressant effects on SA and AV nodal function are
25 mediated by the A₁ receptor; there is no role for the A_{2A} receptor in this response to adenosine. A_{2A} receptors mediate the coronary vasodilatation caused by adenosine. Stimulation of the A₁ adenosine receptor accordingly shortens the duration and decreases the amplitude of the action potential of AV nodal cells, and hence prolongs the refractory period of the AV nodal cell. The consequence of these effects is to limit the number of impulses conducted from the atria
30 to the ventricles. This forms the basis of the clinical utility of A₁ receptor agonists for the treatment of supraventricular tachycardias, including termination of nodal re-entrant tachycardias, and control of ventricular rate during atrial fibrillation and flutter.

 A clinical utility of A₁ agonists therefore is in the treatment of acute and chronic disorders of heart rhythm, especially those diseases characterized by rapid heart rate where the

WO 01/40243

PCT/US00/42509

rate is driven by abnormalities in the sinoatrial, atria, and AV nodal tissues. Such disorders include but are not limited to atrial fibrillation, supraventricular tachycardia and atrial flutter. Exposure to A₁ agonists causes a reduction in the heart rate and a regularization of the abnormal rhythm thereby improving cardiovascular function.

5 A₁ agonists, through their ability to inhibit the effects of catecholamines, decrease cellular cAMP, and thus, should have beneficial effects in the failing heart where increased sympathetic tone increases cellular cAMP levels. The latter has been shown to be associated with increased likelihood of ventricular arrhythmias and sudden death. All of the above concepts are discussed in reviews regarding the effects of adenosine on cardiac
10 electrophysiology (see B. Lerman and L. Belardinelli *Circulation*, Vol. 83 (1991), P 1499-1509 and J. C. Shryock and L. Belardinelli, *Am. J. Cardiology*, Vol. 79 (1997) P 2-10).

A controversial area in the field of A₁ adenosine agonism is that the benefit of preconditioning of the heart prior to ischemia may be due to binding of adenosine to the A₁ receptor. Evidence for this hypothesis comes from a rabbit ischemia model wherein 2-chloro-
15 N6-cyclopentyladenosine (CCPA) and R-PIA were administered prior to ischemia providing protection with respect to infarct size (J. D. Thornton et al. *Circulation* Vol. 85 (1992) 659-665).

A₁ agonists, as a result of their inhibitory action on cyclic AMP generation, have antilipolytic effects in adipocytes that leads to a decreased release of nonesterified fatty acids
20 (NEFA) (E. A. van Schaick et al *J. Pharmacokinetics and Biopharmaceutics*, Vol. 25 (1997) p 673-694 and P. Strong *Clinical Science* Vol. 84 (1993) p. 663-669). Non-insulin-dependent diabetes mellitus (NIDDM) is characterized by an insulin resistance that results in hyperglycemia. Factors contributing to the observed hyperglycemia are a lack of normal glucose uptake and activation of skeletal muscle glycogen synthase (GS). Elevated levels of
25 NEFA have been shown to inhibit insulin-stimulated glucose uptake and glycogen synthesis (D. Thiebaud et al *Metab. Clin. Exp.* Vol. 31 (1982) p 1128-1136 and G. Boden et al *J. Clin. Invest.* Vol. 93 (1994) p 2438-2446). The hypothesis of a glucose fatty acid cycle was proposed by P. J. Randle as early as 1963 (P. J. Randle et al *Lancet* (1963) p. 785-789). A tenet of this hypothesis would be that limiting the supply of fatty acids to the peripheral
30 tissues should promote carbohydrate utilization (P. Strong et al *Clinical Science* Vol. 84 (1993) p. 663-669).

WO 01/40243

PCT/US00/42509

The benefit of an A₁ agonist in central nervous disorders has been reviewed and the content are included herein by reference (L. J. S. Knutsen and T. F. Murray In *Purinergic Approaches in Experimental Therapeutics*, Eds. K. A. Jacobson and M. F. Jarvis (1997) Wiley-Liss, N. Y., P -423-470). Briefly, based on experimental models of epilepsy, a mixed A_{2A}: A₁ agonist, metrifudil, has been shown to be a potent anticonvulsant against seizures induced by the inverse benzodiazepine agonist methyl 6,7-dimethoxy-4-ethyl-beta-carboline-3-carboxylate (DMCM, H. Klitgaard Eur. J. Pharmacol. (1993) Vol. 224 p. 221-228). In other studies using CGS 21680, an A_{2A} agonist, it was concluded that the anticonvulsant activity was attributed to activation of the A₁ receptor (G. Zhang et al. Eur. J. Pharmacol. Vol. 255 (1994) p. 239-243). Furthermore, A₁ adenosine selective agonists have been shown to have anticonvulsant activity in the DMCM model (L. J. S. Knutsen In *Adenosine and Adenine Nucleotides: From Molecular Biology to Integrative Physiology*; eds. L. Belardinelli and A. Pelleg, Kluwer: Boston, 1995, pp 479-487). A second area where an A₁ adenosine agonist has a benefit is in animal models of forebrain ischemia as demonstrated by Knutsen et al (J. Med. Chem. Vol. 42 (1999) p. 3463-3477). The benefit in neuroprotection is believed to be in part due to the inhibition of the release of excitatory amino acids (ibid).

There are a number of full A₁ agonists disclosed in the prior art. However, the agonists disclosed are generally in the forms that are not useful in the mammalian body. Because useful forms of A₁ agonists may not always be stable, soluble or they may have other properties that make their incorporation into therapeutic dosage forms difficult, it is often necessary to identify compositions that are more easily incorporated into therapeutic dosage forms in order to provide the desired therapeutic effect. Also, these agonists fail as useful therapeutics due to side effects caused by the non-selective stimulation of the A₁ adenosine receptor in all biologically available tissues and the desensitization of the desired response preempting their use as chronic agents. Therefore, there remains a need for specific and selective A₁ agonists, precursors and/or pro-drugs that are converted in the body into useful therapeutic compositions.

WO 01/40243

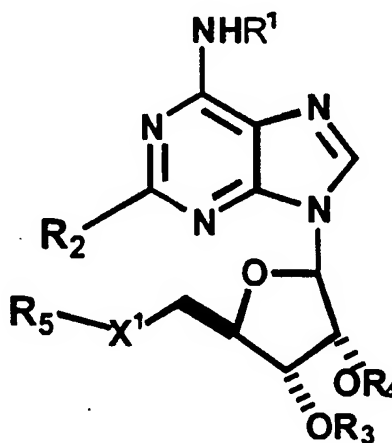
PCT/US00/42509

SUMMARY OF THE INVENTION

In one aspect, this invention includes heterocyclic 5'-thio modified adenosine derivative compositions that are useful partial or full adenosine A₁ receptor agonists.

In another aspect, this invention includes pharmaceutical compositions including one
5 or more heterocyclic 5'-thio modified adenosine derivative compositions that are well tolerated with few side effects.

In still another embodiment, this invention includes heterocyclic 5'-thio modified adenosine derivatives having the formula:



10 In yet another embodiment, this invention includes methods for administering compositions of this invention to mammals, and especially to humans, to stimulate coronary activity, to modify adipocyte function, to treat central nervous system disorders, and to treat diabetic disorders.

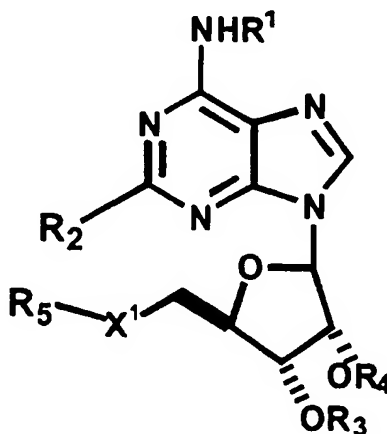
In a further embodiment, this invention is pharmaceutical compositions of matter
15 comprising at least one composition of this invention and one or more pharmaceutical excipients.

WO 01/40243

PCT/US00/42509

DESCRIPTION OF THE CURRENT EMBODIMENT

This invention includes a class of heterocyclic 5'-thio modified adenosine derivatives having the formula having the formula:



5 wherein $X^1 = S, S(O), S(O)_2$;

wherein R^1 is a monocyclic or polycyclic heterocyclic group containing from 3 to 15 carbon atoms wherein at least one carbon atom is substituted with an atom or molecule selected from the group consisting of N, O, P and $S(O)_{0-2}$ and wherein R^1 does not contain an epoxide group, and wherein R_2 is selected from the group consisting of hydrogen, halo, CF_3 , and cyano; wherein R_3 and R_4 are independently selected from the group consisting of hydrogen, and $-(CO)-R'$ and $-(CO)-R''$ wherein R' and R'' are independently selected from the group consisting of C_{1-15} alkyl, C_{2-15} alkenyl, C_{2-15} alkynyl, heterocyclyl, aryl, and heteroaryl, which alkyl, alkenyl, alkynyl, aryl, heterocyclyl, and heteroaryl are optionally substituted with 1 to 3 substituents independently selected from the group of halo, NO_2 , heterocyclyl, aryl, heteroaryl, CF_3 , CN, OR^{20} , SR^{20} , $S(O)R^{22}$, SO_2R^{22} , $SO_2N(R^{20})_2$, $SO_2NR^{20}COR^{22}$, $SO_2NR^{20}CO_2R^{22}$, $SO_2NR^{20}CON(R^{20})_2$, $N(R^{20})_2$, $NR^{20}COR^{22}$, $NR^{20}CO_2R^{22}$, $NR^{20}CON(R^{20})_2$, $NR^{20}C(NR^{20})NHR^{23}$, COR^{20} , CO_2R^{20} , $CON(R^{20})_2$, $CONR^{20}SO_2R^{22}$, $NR^{20}SO_2R^{22}$, $SO_2NR^{20}CO_2R^{22}$, $CONR^{20}SO_2R^{22}$, $OC(O)R^{20}$, $C(O)OCH_2OC(O)R^{20}$, and $OCON(R^{20})_2$ and each optional heteroaryl, aryl, and heterocyclyl substituent is optionally substituted with halo, NO_2 , alkyl, CF_3 , amino, mono- or di-alkylamino, alkyl or aryl or heteroaryl amide, $NR^{20}COR^{22}$, $NR^{20}SO_2R^{22}$, COR^{20} , CO_2R^{20} , $CON(R^{20})_2$, $NR^{20}CON(R^{20})_2$,

WO 01/40243

PCT/US00/42509

OC(O)R²⁰, OC(O)N(R²⁰)₂, SR²⁰, S(O)R²², SO₂R²², SO₂N(R²⁰)₂, CN, or OR²⁰;

wherein R₃ is selected from the group consisting of C₁₋₁₅ alkyl, C₂₋₁₅ alkenyl, C₂₋₁₅ alkynyl, heterocyclyl, aryl, and heteroaryl, wherein alkyl, alkenyl, alkynyl, aryl, heterocyclyl, and heteroaryl are optionally substituted with 1 to 3 substituents independently selected from the group consisting of halo, alkyl, NO₂, heterocyclyl, aryl, heteroaryl, CF₃, CN, OR²⁰, SR²⁰, S(O)₂R²⁰, S(O)R²², SO₂R²², SO₂N(R²⁰)₂, SO₂NR²⁰COR²², SO₂NR²⁰CO₂R²², SO₂NR²⁰CON(R²⁰)₂, P(O)(OR²⁰)₂, N(R²⁰)₂, NR²⁰COR²², NR²⁰CO₂R²², NR²⁰CON(R²⁰)₂, NR²⁰C(NR²⁰)NHR²³, COR²⁰, CO₂R²⁰, CON(R²⁰)₂, CONR²⁰SO₂R²², NR²⁰SO₂R²², SO₂NR²⁰CO₂R²², OCONR²⁰SO₂R²², OC(O)R²⁰, C(O)OCH₂OC(O)R²⁰, and OCON(R²⁰)₂ and wherein optional heteroaryl, aryl, and heterocyclyl substituent is optionally substituted with halo, NO₂, alkyl, CF₃, amino, mono- or di- alkylamino, alkyl or aryl or heteroaryl amide, NR²⁰COR²², NR²⁰SO₂R²², COR²⁰, CO₂R²⁰, CON(R²⁰)₂, NR²⁰CON(R²⁰)₂, OC(O)R²⁰, OC(O)N(R²⁰)₂, SR²⁰, S(O)R²², SO₂R²², SO₂N(R²⁰)₂, CN, or OR²⁰;

wherein R²⁰ is a member selected from the group consisting of H, C1-15 alkyl, C2-15 alkenyl, C2-15 alkynyl, heterocyclyl, aryl, and heteroaryl, which alkyl, alkenyl, alkynyl, heterocyclyl, aryl, and heteroaryl are optionally substituted with 1 to 3 substituents independently selected from halo, alkyl, mono- or dialkylamino, alkyl or aryl or heteroaryl amide, CN, O-C1-C6 alkyl, CF₃, aryl, and heteroaryl; and

R²² is a member selected from the group consisting of C₁₋₁₅ alkyl, C₂₋₁₅ alkenyl, C₂₋₁₅ alkynyl, heterocyclyl, aryl, and heteroaryl, which alkyl, alkenyl, alkynyl, heterocyclyl, aryl, and heteroaryl are optionally substituted with 1 to 3 substituents independently selected from halo, alkyl, mono- or dialkylamino, alkyl or aryl or heteroaryl amide, CN, O-C₁₋₆ alkyl, CF₃, and heteroaryl.

In preferred compositions, X¹=S or SO₂; R₂ is a hydrogen; R₃ and R₄ are each independently selected from the group consisting of hydrogen, -(CO)-R' and -(CO)-R'' wherein R' and R'' are each independently selected from the group consisting of C₁₋₆ alkyl and, more preferably, R₃ and R₄ are each hydrogen; R₅ is selected from the group consisting of C₁₋₈ alkyl, and aryl wherein alkyl, and aryl are optionally substituted with from 1 to 2 substituents independently selected from the group consisting of halo, alkyl, aryl, heteroaryl, CF₃, CN, OR²⁰, S(O)R²², SO₂R²², SO₂N(R²⁰)₂, NR²⁰CON(R²⁰)₂, CO₂R²⁰, CON(R²⁰)₂, and wherein each optional heteroaryl, and aryl substituent is further optionally substituted with

WO 01/40243

PCT/US00/42509

halo, alkyl, CF_3 , CO_2R^{20} , CN, and OR^{20} ; R_{20} is selected from the group consisting of H, C_{1-6} alkyl; and R_{22} is selected from the group consisting of C_{1-6} . In the above compositions, R_5 is more preferably selected from the group consisting of C_{1-8} alkyl, and aryl wherein alkyl, and aryl are optionally substituted with from 1 to 2 substituents independently selected from the group consisting of halo, alkyl, CF_3 , and OR^{20} .

In more preferred compositions, $\text{X}^1=\text{S}$ or SO_2 ; R_2 is a hydrogen; R_3 and R_4 are independently selected from the group consisting of hydrogen, $-(\text{CO})-\text{R}'$ and $-(\text{CO})-\text{R}''$ wherein R' and R'' are each independently selected from the group consisting of C_{1-6} alkyl which alkyl are optionally substituted with 1 substituent selected from the group consisting of aryl, CF_3 , CN, OR^{20} , $\text{N}(\text{R}^{20})_2$, and wherein each optional aryl substituent is further optionally substituted with halo, NO_2 , alkyl, CF_3 ; R_5 is C_{1-8} alkyl, wherein alkyl, is optionally substituted with from 1 to 2 substituents independently selected from the group consisting of halo, alkyl, aryl, heteroaryl, CF_3 , CN, OR^{20} , $\text{S}(\text{O})\text{R}^{22}$, SO_2R^{22} , $\text{SO}_2\text{N}(\text{R}^{20})_2$, $\text{NR}^{20}\text{CON}(\text{R}^{20})_2$, CO_2R^{20} , $\text{CON}(\text{R}^{20})_2$, wherein each optional heteroaryl, and aryl substituent is further optionally substituted with halo, alkyl, CF_3 , CO_2R^{20} , CN, and OR^{20} ; R^{20} is selected from the group consisting of H, C_{1-6} alkyl; and R_{22} is selected from the group consisting of C_{1-6} . In the above compositions, R_5 is more preferably C_{1-8} alkyl that is optionally substituted with from 1 to 2 substituents independently selected from the group consisting of aryl, heteroaryl, OR^{20} , $\text{S}(\text{O})\text{R}^{22}$, CO_2R^{20} , $\text{CON}(\text{R}^{20})_2$, and wherein each optional heteroaryl, and aryl substituent is further optionally substituted with halo, alkyl, CF_3 , CO_2R^{20} , CN, and OR^{20} , and R_5 is even more preferably C_{1-8} alkyl that is optionally substituted with 1 substituent selected from the group consisting of CO_2R^{20} , and $\text{CON}(\text{R}^{20})_2$, and R_5 is even more preferably C_{1-6} alkyl and most preferably methyl or ethyl or isopropyl. Also in the above compositions, R_3 and R_4 are more preferably each hydrogen and R_{20} is more preferably selected from the group consisting of H, and methyl.

In another class of preferred compositions, R_2 is a hydrogen; R_3 and R_4 are each independently selected from the group consisting of hydrogen, $-(\text{CO})-\text{R}'$ and $-(\text{CO})-\text{R}''$ wherein each R' and R'' are independently selected from the group consisting of C_{1-6} alkyl, and aryl, which alkyl and aryl are optionally substituted with from 1 to 2 substituents independently selected from the group of halo, NO_2 , aryl, CF_3 , CN, OR^{20} , $\text{N}(\text{R}^{20})_2$, $\text{S}(\text{O})\text{R}^{22}$, SO_2R^{22} , and wherein each optional aryl substituent is further optionally substituted with halo,

WO 01/40243

PCT/US00/42509

NO₂, alkyl, CF₃; R₃ is selected from the group consisting of, aryl, and heteroaryl, wherein aryl, and heteroaryl are optionally substituted with from 1 to 3 substituents independently selected from the group consisting of halo, alkyl, aryl, heteroaryl, CF₃, CN, OR²⁰, SR²⁰, N(R²⁰)₂, S(O)R²², SO₂R²², SO₂N(R²⁰)₂, NR²⁰CO₂R²², NR²⁰CON(R²⁰)₂, CO₂R²⁰, CON(R²⁰)₂, and wherein

5 each optional heteroaryl, and aryl substituent is further optionally substituted with halo, alkyl, CF₃, CO₂R²⁰, CON(R²⁰)₂, S(O)R²², SO₂R²², SO₂N(R²⁰)₂, CN, or OR²⁰; R²⁰ is selected from the group consisting of H, C₁₋₆ alkyl, and aryl, which alkyl and aryl are optionally substituted with 1 substituent selected from halo, alkyl, mono- or dialkylamino, CN, O-C₁₋₆ alkyl, CF₃; and R²² is selected from the group consisting of C₁₋₆ alkyl and aryl, which alkyl and aryl are optionally

10 substituted with 1 substituent selected from halo, alkyl or CN, O-C₁₋₆ alkyl, and CF₃. In the above compositions, X¹ is preferably S; R₃ and R₄ are more preferably hydrogen; R₅ is more preferably selected from the group consisting of, aryl, and heteroaryl, wherein aryl, and heteroaryl are optionally substituted with from 1 to 3 substituents independently selected from the group consisting of halo, alkyl, CF₃, CN, OR²⁰, SR²⁰, CO₂R²⁰, CON(R²⁰)₂. Even more

15 preferably R₅ is aryl that is optionally substituted with from 1 to 2 substituents independently selected from the group consisting of halo, alkyl, CF₃, OR²⁰, CO₂R²⁰, CON(R²⁰)₂. And most preferably, R₅ is phenyl that is optionally substituted with a substituent selected from the group consisting of methoxy, chloro, fluoro, methyl, and trifluoromethyl. In the compounds above, R²⁰ is preferably selected from the group consisting of H, C₁₋₃ alkyl and most

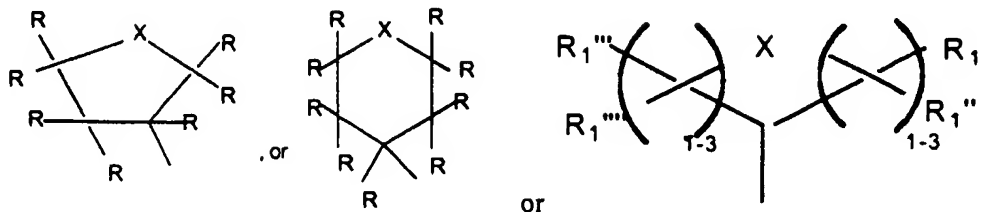
20 preferably H or methyl while R₂₂ is preferably selected from the group consisting of C₁₋₆ alkyl.

In the compositions of this invention, R₁ is preferably mono or polysubstituted with one or more compounds selected from the group consisting of halogen, oxo, hydroxyl, lower alkyl, substituted lower alkyl, alkoxy, aryl, acyl, aryloxy, carboxyl, substituted aryl, heterocycle, heteroaryl, substituted heteroaryl, cycloalkyl, substituted cycloalkyl, nitro, cyano

25 and mixtures thereof. More preferably, R₁ is a monocyclic, bicyclic, or tricyclic cycloalkyl group containing from 3 to 15 carbon atoms wherein at least one carbon atom is substituted with an atom or molecule selected from the group consisting of O or S-(O)₀₋₂. Some examples of preferred R₁ moieties include:

WO 01/40243

PCT/US00/42509



wherein R_1' , R_1'' , R_1''' , and R_1'''' may each individually be selected from the group halogen, hydroxyl, lower alkyl, substituted lower alkyl, alkoxy, aryl, acyl, aryloxy, carboxyl, substituted aryl, heterocycle, heteroaryl, substituted heteroaryl, cycloalkyl, substituted cycloalkyl, nitro, and cyano, and X is O, or S $(-O)_{0.2}$, alternately, R_1''' and R_1'''' may be a single oxygen atom. More preferably, R_1' , R_1'' , R_1''' , and R_1'''' are each individually selected from the group hydrogen, lower alkyl, and substituted lower alkyl. In the compositions above, each R is individually selected from the group consisting of H, lower alkyl, and substituted lower alkyl and wherein X is O, or S $(-O)_{0.2}$.

Most preferred compounds of this invention include, 2-{6-[(3R)oxolan-3-yl]amino}purin-9-yl}(4S,5S,2R,3R)-5-(methylthiomethyl)oxolane-3,4-diol ; 2-{6-[(3R)oxolan-3-yl]amino}purin-9-yl}(4S,5S,2R,3R)-5-[(Ethylthio)methyl]oxolane-3,4-diol; 2-{6-[(3R)oxolan-3-yl]amino}purin-9-yl}(4S,5S,2R,3R)-5-[(Methylethylthio)methyl]oxolane-3,4-diol; 2-{6-[(3R)oxolan-3-yl]amino}purin-9-yl}(4S,5S,2R,3R)-5-[(phenylthiomethyl)oxolane-3,4-diol; 2-{6-[(3R)oxolan-3-yl]amino}purin-9-yl}(4S,5S,2R,3R)-5-[(4-Methoxyphenylthio)methyl]oxolane-3,4-diol; 2-{6-[(3R)oxolan-3-yl]amino}purin-9-yl}(4S,5S,2R,3R)-5-[(4-chlorophenylthio)methyl]oxolane-3,4-diol; 2-{6-[(3R)oxolan-3-yl]amino}purin-9-yl}(4S,5S,2R,3R)-5-[(4-fluorophenylthio)methyl]oxolane-3,4-diol; 2-{6-[(3R)oxolan-3-yl]amino}purin-9-yl}(4S,5S,2R,3R)-5-[(4-methylphenylthio)methyl]oxolane-3,4-diol; 2-{6-[(3R)oxolan-3-yl]amino}purin-9-yl}(4S,5S,2R,3R)-5-[(4-(trifluoromethyl)phenylthio)methyl]oxolane-3,4-diol; 2-{6-[(3R)oxolan-3-yl]amino}purin-9-yl}(4S,5S,2R,3R)-5-[(2-Methoxyphenylthio)methyl]oxolane-3,4-diol; and (5-{6-[(3R)oxolan-3-yl]amino}purin-9-yl)(2S,3S,4R,5R)-3,4-dihydroxyoxolan-2-yl)(ethylsulfonyl)methane.

The following definitions apply to terms as used herein.

"Halo" or "Halogen" - alone or in combination means all halogens, that is, chloro (Cl),

WO 01/40243

PCT/US00/42509

fluoro (F), bromo (Br), iodo (I).

“Hydroxyl” refers to the group -OH.

“Thiol” or “mercapto” refers to the group -SH.

“Alkyl” - alone or in combination means an alkane-derived radical containing from 1
5 to 20, preferably 1 to 15, carbon atoms (unless specifically defined). It is a straight chain
alkyl, branched alkyl or cycloalkyl. Preferably, straight or branched alkyl groups containing
from 1-15, more preferably 1 to 8, even more preferably 1-6, yet more preferably 1-4 and
most preferably 1-2, carbon atoms, such as methyl, ethyl, propyl, isopropyl, butyl, t-butyl and
the like. The term “lower alkyl” is used herein to describe the straight chain alkyl groups
10 described immediately above. Preferably, cycloalkyl groups are monocyclic, bicyclic or
tricyclic ring systems of 3-8, more preferably 3-6, ring members per ring, such as cyclopropyl,
cyclopentyl, cyclohexyl, adamantyl and the like. Alkyl also includes a straight chain or
branched alkyl group that contains or is interrupted by a cycloalkyl portion. The straight
chain or branched alkyl group is attached at any available point to produce a stable compound.
15 Examples of this include, but are not limited to, 4-(isopropyl)-cyclohexylethyl or 2-methyl-
cyclopropylpentyl. A substituted alkyl is a straight chain alkyl, branched alkyl, or cycloalkyl
group defined previously, independently substituted with 1 to 3 groups or substituents of halo,
hydroxy, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, acyloxy, aryloxy, heteroaryloxy,
amino optionally mono- or di-substituted with alkyl, aryl or heteroaryl groups, amidino, urea
20 optionally substituted with alkyl, aryl, heteroaryl or heterocyclyl groups, aminosulfonyl
optionally N-mono- or N,N-di-substituted with alkyl, aryl or heteroaryl groups,
alkylsulfonylamino, arylsulfonylamino, heteroarylsulfonylamino, alkylcarbonylamino,
arylcarbonylamino, heteroarylcarbonylamino, or the like.

“Alkenyl” - alone or in combination means a straight, branched, or cyclic hydrocarbon
25 containing 2-20, preferably 2-17, more preferably 2-10, even more preferably 2-8, most
preferably 2-4, carbon atoms and at least one, preferably 1-3, more preferably 1-2, most
preferably one, carbon to carbon double bond. In the case of a cycloalkyl group, conjugation
of more than one carbon to carbon double bond is not such as to confer aromaticity to the ring.
Carbon to carbon double bonds may be either contained within a cycloalkyl portion, with the
30 exception of cyclopropyl, or within a straight chain or branched portion. Examples of alkenyl
groups include ethenyl, propenyl, isopropenyl, butenyl, cyclohexenyl, cyclohexenylalkyl and

WO 01/40243

PCT/US00/42509

the like. A substituted alkenyl is the straight chain alkenyl, branched alkenyl or cycloalkenyl group defined previously, independently substituted with 1 to 3 groups or substituents of halo, hydroxy, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, acyloxy, aryloxy, heteroaryloxy, amino optionally mono- or di-substituted with alkyl, aryl or heteroaryl groups, amidino, urea
 5 optionally substituted with alkyl, aryl, heteroaryl or heterocyclyl groups, aminosulfonyl optionally N-mono- or N,N-di-substituted with alkyl, aryl or heteroaryl groups, alkylsulfonylamino, arylsulfonylamino, heteroarylsulfonylamino, alkylcarbonylamino, arylcarbonylamino, heteroarylcarbonylamino, carboxy, alkoxycarbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, or the like attached at any available point to produce a stable
 10 compound.

"Alkynyl" - alone or in combination means a straight or branched hydrocarbon containing 2-20, preferably 2-17, more preferably 2-10, even more preferably 2-8, most preferably 2-4, carbon atoms containing at least one, preferably one, carbon to carbon triple bond. Examples of alkynyl groups include ethynyl, propynyl, butynyl and the like. A
 15 substituted alkynyl refers to the straight chain alkynyl or branched alkenyl defined previously, independently substituted with 1 to 3 groups or substituents of halo, hydroxy, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, acyloxy, aryloxy, heteroaryloxy, amino optionally mono- or di-substituted with alkyl, aryl or heteroaryl groups, amidino, urea optionally substituted with alkyl, aryl, heteroaryl or heterocyclyl groups, aminosulfonyl optionally N-
 20 mono- or N,N-di-substituted with alkyl, aryl or heteroaryl groups, alkylsulfonylamino, arylsulfonylamino, heteroarylsulfonylamino, alkylcarbonylamino, arylcarbonylamino, heteroarylcarbonylamino, or the like attached at any available point to produce a stable compound.

"Alkyl alkenyl" refers to a group $-R-CR'=CR''R'''$, where R is lower alkyl, or
 25 substituted lower alkyl, R', R'', R''' may independently be hydrogen, halogen, lower alkyl, substituted lower alkyl, acyl, aryl, substituted aryl, hetaryl, or substituted hetaryl as defined below.

"Alkyl alkynyl" refers to a groups $-RCCR'$ where R is lower alkyl or substituted lower alkyl, R' is hydrogen, lower alkyl, substituted lower alkyl, acyl, aryl, substituted aryl,
 30 hetaryl, or substituted hetaryl as defined below.

"Alkoxy" denotes the group $-OR$, where R is lower alkyl, substituted lower alkyl, acyl,

WO 01/40243

PCT/US00/42509

aryl, substituted aryl, aralkyl, substituted aralkyl, heteroalkyl, heteroarylalkyl, cycloalkyl, substituted cycloalkyl, cycloheteroalkyl, or substituted cycloheteroalkyl as defined.

“Alkylthio” denotes the group $-SR$, $-S(O)_{n-1,2}-R$, where R is lower alkyl, substituted lower alkyl, aryl, substituted aryl, aralkyl or substituted aralkyl as defined herein.

5 “Acyl” denotes groups $-C(O)R$, where R is hydrogen, lower alkyl substituted lower alkyl, aryl, substituted aryl and the like as defined herein.

“Aryloxy” denotes groups $-OAr$, where Ar is an aryl, substituted aryl, heteroaryl, or substituted heteroaryl group as defined herein.

10 “Amino” denotes the group NRR' , where R and R' may independently be hydrogen, lower alkyl, substituted lower alkyl, aryl, substituted aryl, hetaryl, or substituted hetaryl as defined herein or acyl.

“Amido” denotes the group $-C(O)NRR'$, where R and R' may independently be hydrogen, lower alkyl, substituted lower alkyl, aryl, substituted aryl, hetaryl, substituted hetaryl as defined herein.

15 “Carboxyl” denotes the group $-C(O)OR$, where R is hydrogen, lower alkyl, substituted lower alkyl, aryl, substituted aryl, hetaryl, and substituted hetaryl as defined herein.

“Aryl” - alone or in combination means phenyl or naphthyl optionally carbocyclic fused with a cycloalkyl of preferably 5-7, more preferably 5-6, ring members and/or optionally substituted with 1 to 3 groups or substituents of halo, hydroxy, alkoxy, alkylthio, 20 alkylsulfinyl, alkylsulfonyl, acyloxy, aryloxy, heteroaryloxy, amino optionally mono- or di-substituted with alkyl, aryl or heteroaryl groups, amidino, urea optionally substituted with alkyl, aryl, heteroaryl or heterocyclyl groups, aminosulfonyl optionally N-mono- or N,N-di-substituted with alkyl, aryl or heteroaryl groups, alkylsulfonylamino, arylsulfonylamino, heteroarylsulfonylamino, alkylcarbonylamino, arylcarbonylamino, heteroarylcarbonylamino, 25 or the like.

“Substituted aryl” refers to aryl optionally substituted with one or more functional groups, e.g., halogen, lower alkyl, lower alkoxy, alkylthio, acetylene, amino, amido, carboxyl, hydroxyl, aryl, aryloxy, heterocycle, hetaryl, substituted hetaryl, nitro, cyano, thiol, sulfamido and the like.

30 “Heterocycle” refers to a saturated, unsaturated, or aromatic carbocyclic group having a single ring (e.g., morpholino, pyridyl or furyl) or multiple condensed rings (e.g.,

WO 01/40243

PCT/US00/42509

naphthpyridyl, quinoxalyl, quinolinyl, indolizinyll or benzo[b]thienyl) and having at least one hetero atom, such as N, O or S, within the ring, which can optionally be unsubstituted or substituted with, *e.g.*, halogen, lower alkyl, lower alkoxy, alkylthio, acetylene, amino, amido, carboxyl, hydroxyl, aryl, aryloxy, heterocycle, hetaryl, substituted hetaryl, nitro, cyano, thiol, sulfamido and the like.

"Heteroaryl" - alone or in combination means a monocyclic aromatic ring structure containing 5 or 6 ring atoms, or a bicyclic aromatic group having 8 to 10 atoms, containing one or more, preferably 1-4, more preferably 1-3, even more preferably 1-2, heteroatoms independently selected from the group O, S, and N, and optionally substituted with 1 to 3 groups or substituents of halo, hydroxy, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, acyloxy, aryloxy, heteroaryloxy, amino optionally mono- or di-substituted with alkyl, aryl or heteroaryl groups, amidino, urea optionally substituted with alkyl, aryl, heteroaryl or heterocyclyl groups, aminosulfonyl optionally N-mono- or N,N-di-substituted with alkyl, aryl or heteroaryl groups, alkylsulfonylamino, arylsulfonylamino, heteroarylsulfonylamino, alkylcarbonylamino, arylcarbonylamino, heteroarylcarbonylamino, or the like. Heteroaryl is also intended to include oxidized S or N, such as sulfinyl, sulfonyl and N-oxide of a tertiary ring nitrogen. A carbon or nitrogen atom is the point of attachment of the heteroaryl ring structure such that a stable aromatic ring is retained. Examples of heteroaryl groups are pyridinyl, pyridazinyl, pyrazinyl, quinazolinyl, purinyl, indolyl, quinolinyl, pyrimidinyl, pyrrolyl, oxazolyl, thiazolyl, thienyl, isoxazolyl, oxathiadiazolyl, isothiazolyl, tetrazolyl, imidazolyl, triazinyl, furanyl, benzofuryl, indolyl and the like. A substituted heteroaryl contains a substituent attached at an available carbon or nitrogen to produce a stable compound.

"Heterocyclyl" - alone or in combination means a non-aromatic cycloalkyl group having from 5 to 10 atoms in which from 1 to 3 carbon atoms in the ring are replaced by heteroatoms of O, S or N, and are optionally benzo fused or fused heteroaryl of 5-6 ring members and/or are optionally substituted as in the case of cycloalkyl. Heterocyclyl is also intended to include oxidized S or N, such as sulfinyl, sulfonyl and N-oxide of a tertiary ring nitrogen. The point of attachment is at a carbon or nitrogen atom. Examples of heterocyclyl groups are tetrahydrofuranyl, dihydropyridinyl, piperidinyl, pyrrolidinyl, piperazinyl,

WO 01/40243

PCT/US00/42509

dihydrobenzofuryl, dihydroindolyl, and the like. A substituted heterocyclyl contains a substituent nitrogen attached at an available carbon or nitrogen to produce a stable compound.

“Substituted heteroaryl” refers to a heterocycle optionally mono or poly substituted with one or more functional groups, *e.g.*, halogen, lower alkyl, lower alkoxy, alkylthio, acetylene, amino, amido, carboxyl, hydroxyl, aryl, aryloxy, heterocycle, substituted heterocycle, hetaryl, substituted hetaryl, nitro, cyano, thiol, sulfamido and the like.

“Aralkyl” refers to the group -R-Ar where Ar is an aryl group and R is lower alkyl or substituted lower alkyl group. Aryl groups can optionally be unsubstituted or substituted with, *e.g.*, halogen, lower alkyl, alkoxy, alkylthio, acetylene, amino, amido, carboxyl, hydroxyl, aryl, aryloxy, heterocycle, substituted heterocycle, hetaryl, substituted hetaryl, nitro, cyano, thiol, sulfamido and the like.

“Heteroalkyl” refers to the group -R-Het where Het is a heterocycle group and R is a lower alkyl group. Heteroalkyl groups can optionally be unsubstituted or substituted with *e.g.*, halogen, lower alkyl, lower alkoxy, alkylthio, acetylene, amino, amido, carboxyl, aryl, aryloxy, heterocycle, substituted heterocycle, hetaryl, substituted hetaryl, nitro, cyano, thiol, sulfamido and the like.

“Heteroarylalkyl” refers to the group -R-HetAr where HetAr is an heteroaryl group and R lower alkyl or substituted lower alkyl. Heteroarylalkyl groups can optionally be unsubstituted or substituted with, *e.g.*, halogen, lower alkyl, substituted lower alkyl, alkoxy, alkylthio, acetylene, aryl, aryloxy, heterocycle, substituted heterocycle, hetaryl, substituted hetaryl, nitro, cyano, thiol, sulfamido and the like.

“Cycloalkyl” refers to a divalent cyclic or polycyclic alkyl group containing 3 to 15 carbon atoms.

“Substituted cycloalkyl” refers to a cycloalkyl group comprising one or more substituents with, *e.g.*, halogen, lower alkyl, substituted lower alkyl, alkoxy, alkylthio, acetylene, aryl, aryloxy, heterocycle, substituted heterocycle, hetaryl, substituted hetaryl, nitro, cyano, thiol, sulfamido and the like.

“Cycloheteroalkyl” refers to a cycloalkyl group wherein one or more of the ring carbon atoms is replaced with a heteroatom (*e.g.*, N, O, S or P).

Substituted cycloheteroalkyl” refers to a cycloheteroalkyl group as herein defined which contains one or more substituents, such as halogen, lower alkyl, lower alkoxy,

WO 01/40243

PCT/US00/42509

alkylthio, acetylene, amino, amido, carboxyl, hydroxyl, aryl, aryloxy, heterocycle, substituted heterocycle, hetaryl, substituted hetaryl, nitro, cyano, thiol, sulfamido and the like.

“Alkyl cycloalkyl” denotes the group -R-cycloalkyl where cycloalkyl is a cycloalkyl group and R is a lower alkyl or substituted lower alkyl. Cycloalkyl groups can optionally be
5 unsubstituted or substituted with *e.g.* halogen, lower alkyl, lower alkoxy, alkylthio, acetylene, amino, amido, carboxyl, hydroxyl, aryl, aryloxy, heterocycle, substituted heterocycle, hetaryl, substituted hetaryl, nitro, cyano, thiol, sulfamido and the like.

“Alkyl cycloheteroalkyl” denotes the group -R-cycloheteroalkyl where R is a lower alkyl or substituted lower alkyl. Cycloheteroalkyl groups can optionally be unsubstituted or
10 substituted with *e.g.* halogen, lower alkyl, lower alkoxy, alkylthio, amino, amido, carboxyl, acetylene, hydroxyl, aryl, aryloxy, heterocycle, substituted heterocycle, hetaryl, substituted hetaryl, nitro, cyano, thiol, sulfamido and the like.

The compounds of this invention can be prepared as outlined in the schemes 1-5 below. A general outline for the preparation of V and VI is shown in Scheme 1. Compound I
15 can be prepared, following the procedures reported earlier (U.S. Patent No. 5,789,416, the specification of which is incorporated herein by reference), by reacting 6-chloropurine riboside 1 with a primary amine R^1NH_2 . The 2', 3' hydroxy groups can be protected as acetonide by reacting I with 2,2'-dimethoxypropane in the presence of a catalytic amount of TsOH [Evans, Parrish and Long Carbohydrat. Res., 3, 453 (1967)] to give II. Activation of
20 the 5'-hydroxyl of II with MsCl in pyridine can give the 5'-mesylate III. Displacement of the 5'-mesylate with R^5SNa can give sulfides with the general formula IV. Treatment of IV with an acid can free the 2', 3' hydroxyl groups to give sulfide derivatives with the general formula V. Esterification of V can afford 2', 3' diesters with the general formula VI.

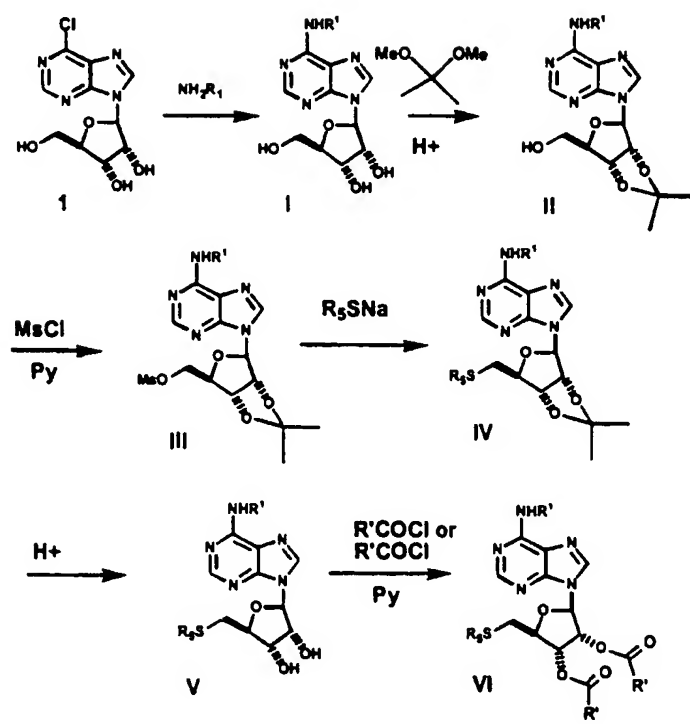
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WO 01/40243

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Scheme 1

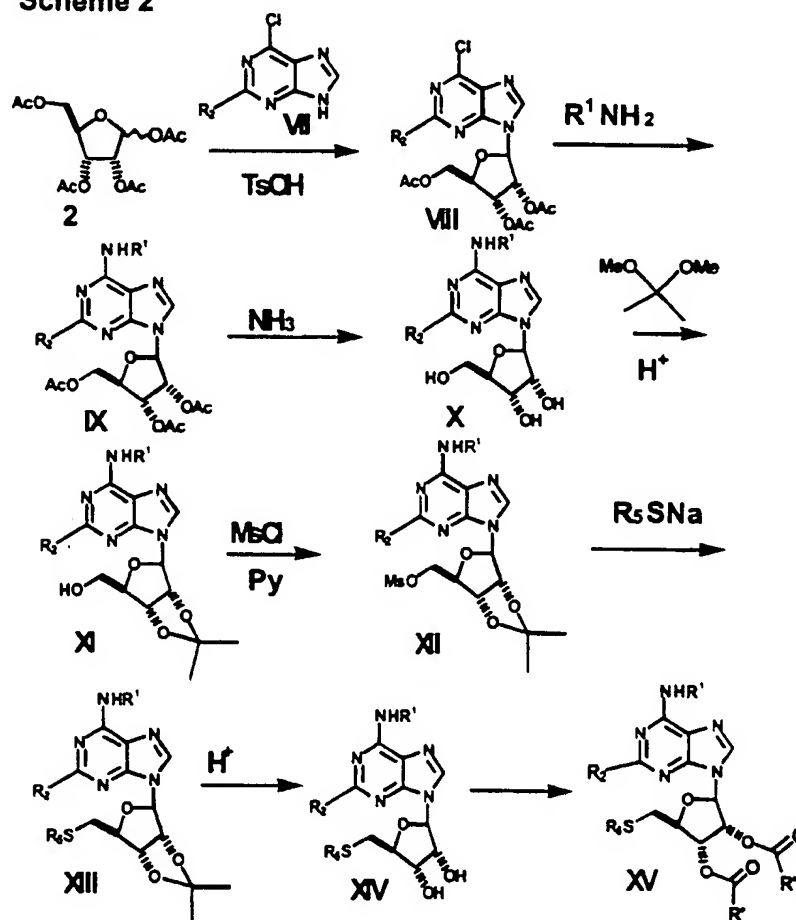


WO 01/40243

PCT/US00/42509

The 2-substituted derivatives with the general formula XV can be prepared as shown in Scheme 2. Condensation of 1,2,3,5-tetraacetylribofuranoside **2** with 2-substituted-6-chloropurine **VII** can give 2-substituted-6-chloropurineriboside triacetate **VIII** which on reaction with a primary amine R^1NH_2 can give 2-substituted-6-alkylamino derivatives **IX**. Hydrolysis of the acetates followed by protection of the 2', 3' hydroxy groups as an acetonide can give **XI**. Activation of the 5'-hydroxyl of **XI** with MsCl in pyridine can give the 5'-mesylate **XII**. Displacement of the 5'-mesylate with R^5SNa can give sulfides with the general

Scheme 2



formula **XIII** that can be deprotected to give sulfides with general formula **XIV**. Esterification at the 2', 3' positions can afford the 2', 3'-diesters with the general formula XV.

10 Oxidation of sulfides with the general formula V, VI, XIV, XV (Scheme 3) with an oxidizing agent (Drabowicz, et.al. The chemistry of sulfones and sulfoxides, Wiley, New

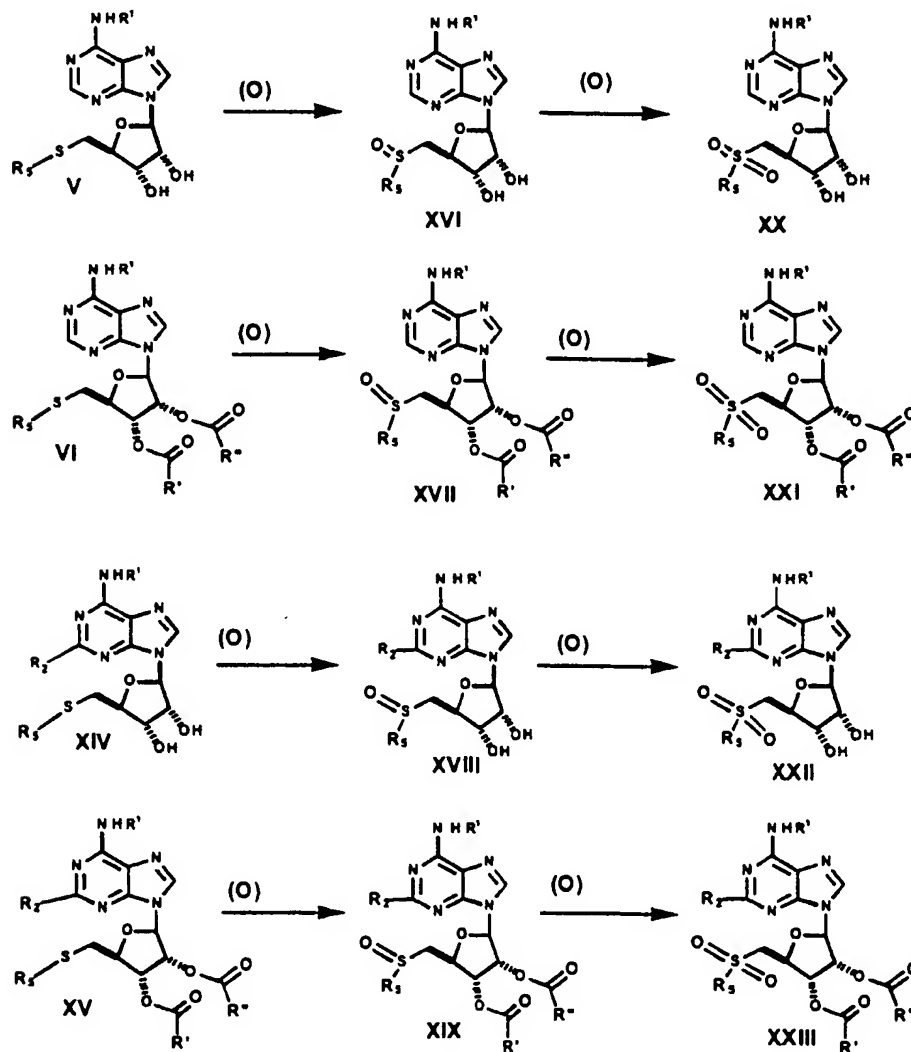
WO 01/40243

PCT/US00/42509

York, 1988, 233-378) can afford corresponding sulfoxides with the general formula XVI, XVII, XVIII, XIX. These sulfoxides on further oxidation can afford sulfones with the general formula XX, XXI, XXII, XXIII.

5

Scheme 3

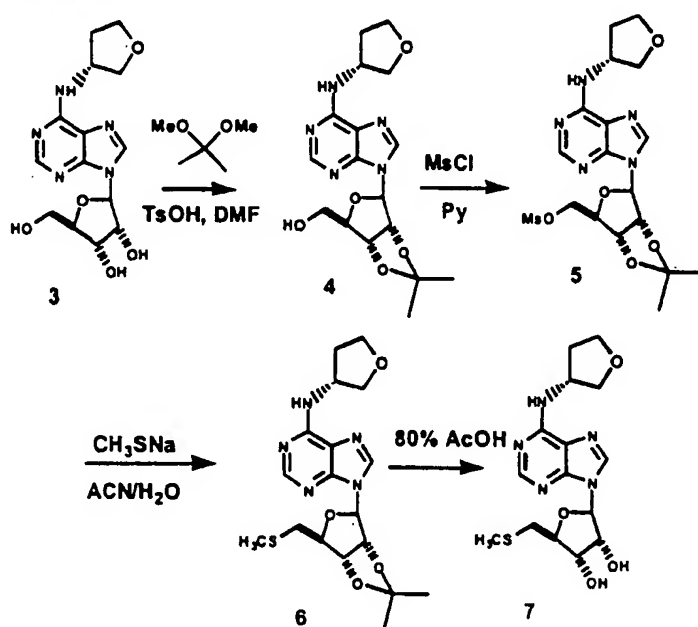


WO 01/40243

PCT/US00/42509

An example of a specific synthesis of one of the compounds of this invention is shown in Scheme 4. Preparation of compound 7 starting from compound 3 is shown in scheme 3. Compound 3 was prepared from 6-chloropurineriboside 1 and 3-(R)-aminotetrahydrofuran following the procedure reported previously (See U.S. Patent No. 5,789,164). Protection of the 2' and 3' hydroxyls with dimethoxypropane in the presence of TsOH(cat.) gave acetoneide 4. Reaction of 4 with MsCl in pyridine at 0 °C gave mesylate 5 which on displacement with sodium methanethiolate in an acetonitrile/water mixture gave sulfide 6. Deprotection of 6 with 80% acetic acid /water gave the target compound 7.

Scheme 4



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PCT/US00/42509

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Chemical reaction scheme showing the oxidation of compound **8** to compound **9**. Compound **8** is a purine derivative with a morpholine group at position 6, a 2-ethylthio group at position 9, and a 2,3-dihydroxypropyl group at position 1. Oxidation with Oxone in MeOH yields compound **9**, where the ethylthio group is converted to an ethanesulfonyl group.

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WO 01/40243

PCT/US00/42509

If a compound of this invention contains a basic group, then corresponding acid addition salt may be prepared. Acid addition salts of the compounds are prepared in a standard manner in a suitable solvent from the parent compound and an excess of acid, such as hydrochloric, hydrobromic, sulfuric, phosphoric, acetic, maleic, succinic, or methanesulfonic. The hydrochloric salt form is especially useful. If a compound of this invention contains an acidic group, then corresponding cationic salts may be prepared. Typically the parent compound is treated with an excess of an alkaline reagent, such as hydroxide, carbonate or alkoxide, containing the appropriate cation. Cations such as Na^+ , K^+ , Ca^{+2} and NH_4^+ are examples of cations present in pharmaceutically acceptable salts. Certain of the compounds form inner salts or zwitterions which may also be acceptable.

The compositions of this invention are useful for treating a variety of mammalian disorders and preferably human disorders that are mediated by an A_1 adenosine receptor. For example, the compositions of this invention are useful for modifying cardiac activity in mammals experiencing a coronary electrical disorder that can be treated by stimulating an A_1 adenosine receptor. Examples of coronary electrical disorders that can be treated by the compositions of this invention include supraventricular tachycardias, atrial fibrillation, atrial flutter, and AV nodal re-entrant tachycardia. Furthermore, orally active A_1 agonists of this invention that demonstrate an excellent safety profile in treating supraventricular arrhythmias may also be used as a prophylactic for those at high risk of a myocardial ischemia.

The compositions of this invention are also useful for modifying adipocyte function by stimulating an A_1 adenosine receptor that leads to diminished release of NEFA and increased release of leptin. Disease states related to adipocyte function that can be modified using compositions of this invention include diabetes, and obesity.

WO 01/40243

PCT/US00/42509

In skeletal muscle cells, A₁ AdoR agonists mediate a synergistic stimulation of glucose uptake and transport by insulin (Vergauwen, L. *et al*, *J. Clin. Invest.* 1994, 93, 974-81; Challiss, R.A. *et al*, *Eur.J.Pharmacol.*, 1992, 226, 121-8). Another therapeutic utility of compositions of this invention is more efficient regulation of glucose and a decrease of circulating insulin in patients afflicted with diabetes.

The A₁ receptor agonist, R-PIA, has been shown to increase the leptin released from white adipocytes and augment insulin-stimulated leptin production (M. Ozeck Master's Thesis Univ. of Florida 1999 with L. Belardinelli). Evidence suggests that catecholamines inhibit the production of leptin from adipocytes through activation of β -adrenergic receptors.

The anti- β -adrenergic effects of A₁ agonists on the adipocytes are believed to play a role in the increased release of leptin. The functional role of leptin is multifaceted including decreased appetite, stimulated energy utilization, and increased fertility.

The compositions of this invention may also be used to provide central nervous system neuroprotection by stimulating an A₁ adenosine receptor. Central nervous system disorders that may be treated using the compositions of this invention include epilepsy, and stroke.

In the kidney, there is evidence that stimulation of the A₁ AdoR promotes sodium retention, promotes exchange of sodium in urine for potassium, and reduces glomerular filtration rate as sodium excretion increases (Gellai, M. *et al*, *JPET*, 1998, 286, 1191-6; Wilcox, C.S. *et al*, *J.Am.Soc.Nephrol.*, 1999, 10, 714-720). It is believed that these responses are elicited by chronic local production of adenosine. That is, in the kidney there is a tonic effect of adenosine to stimulate the A₁ AdoR. Another clinical utility of compositions of this invention, therefore, is the selective antagonism of the A₁ AdoR in the kidney to inhibit sodium retention, inhibit the exchange of sodium for potassium, and preserve kidney

WO 01/40243

PCT/US00/42509

glomerular filtration rate when sodium excretion rises to yield a potassium sparing diuretic that preserves renal function.

The compositions of this invention are further useful for providing cardiomyocyte protection from ischemic events by stimulating an A₁ adenosine receptor. Ischemic events
5 treatable using the compositions of this invention include stable angina, unstable angina, cardiac transplant, and myocardial infarction.

An important aspect of compounds of this invention is that each compound has an intrinsic efficacy associated with it (for a discussion see T. P. Kenakin Stimulus Response Mechanisms. In Pharmacological Analysis of Drug-Receptor Interaction, Ed. Kenakin, T.P.
10 New York: Raven Press, p 39-68). This intrinsic efficacy is not defined by it's affinity for the receptor, but it is defined as the quantitative effect of the compound to activate a given effector system (eg. cAMP production) in a given cell type. The intrinsic efficacy of a given compound may vary from cell type to cell type and/or from effector system to effector system.

When a compound has an intrinsic efficacy lower than a full agonist (i.e. submaximal) than
15 the agonist is called a partial agonist. Thus, a partial agonist is a molecule that binds to a receptor and elicits a response that is smaller than that of a full agonist (submaximal), but also competitively antagonizes the response(s) elicited by a full agonist. The tonic action of adenosine with respect to kidney function is a prime example where a partial A₁ agonist be expected to act as antagonists (e.g. adenosine). The tonic action of adenosine with respect to
20 kidney function is a prime example where a partial A₁ agonist could be expected to act as an antagonist. The compounds of this invention are believed to have therapeutically useful affinities for the adenosine A₁ receptor, and they will have a range of intrinsic efficacies from full agonist to partial agonist. That is, some compounds may have no effect with respect to a

WO 01/40243

PCT/US00/42509

given effector system in a given cell type, but be a full agonist in another cell type and/or effector system. The reason for such variable pharmacological behavior relates to the magnitude of the receptor reserve for the A₁ adenosine receptor in any given cell type (eg. AV nodal cells vs. adipocytes) and for a given response. The receptor reserve (spare receptor capacity) is the total number of receptors minus the fraction of receptors that is required to induce the maximal response using a full agonist (L. E. Limbird, *Cell Surface Receptors: A Short Course on Theory and Methods*, Kluwer Acad. Pub. 1996, Boston, Mass.). Therefore, the agonist could be a full agonist at eliciting a response, and a partial agonist for eliciting another response in other tissue or cells and still be an antagonist or lack activity for a third response in another tissue or cell. Consequently, a partial agonist targeted to a selected target is likely to cause fewer side effects than a full agonist. As a corollary, a full agonist elicits all the effects mediated by the respective receptor, whereas this is not necessarily the case of a partial agonist. The compounds of this invention based on their affinity for the A₁ receptor and their potency and selectivity to elicit A₁ receptor mediated responses have the potential for therapeutic intervention in the multiple disease states described above.

Partial A₁ agonists may have an added benefit for chronic therapy because they will be less likely to induce desensitization of the A₁ receptor (R. B. Clark, B. J. Knoll, R. Barber *TIPS*, Vol. 20 (1999) p. 279-286) and to cause side effects. Chronic administration of a full agonist (R-N6-phenylisopropyladenosine, R-PIA) for 7 days led to a desensitization of the A₁ receptor in terms of the dromotropic response in guinea pigs (note: a decrease in receptor number was observed – D. M. Dennis, J. C. Shryock, L. Belardinelli *JPET*, Vol. 272 (1995) p. 1024-1035). The A₁ agonist induced inhibitory effect on the production of cAMP by adenylate cyclase in adipocytes has been shown to desensitize upon chronic treatment with an

WO 01/40243

PCT/US00/42509

A₁ agonist as well (W. J. Parsons and G. L. Stiles J. Biol. Chem. Vol. 262 (1987) p. 841-847).

The compositions of this invention may be administered orally, intravenously, through the epidermis, bolus, nasally, by inhalation or by any other means known in the art for administering a therapeutic agents. The method of treatment comprises the administration of
5 an effective quantity of the chosen compound, preferably dispersed in a pharmaceutical carrier. Dosage units of the active ingredient are generally selected from the range of 0.01 to 100 mg/kg, but will be readily determined by one skilled in the art depending upon the route of administration, age and condition of the patient.

Pharmaceutical compositions including the compounds of this invention, and/or
10 derivatives thereof, may be formulated as solutions or lyophilized powders for parenteral administration. Powders may be reconstituted by addition of a suitable diluent or other pharmaceutically acceptable carrier prior to use. If used in liquid form the compositions of this invention are preferably incorporated into a buffered, isotonic, aqueous solution. Examples of suitable diluents are normal isotonic saline solution, standard 5% dextrose in
15 water and buffered sodium or ammonium acetate solution. Such liquid formulations are suitable for parenteral administration, but may also be used for oral administration. It may be desirable to add excipients such as polyvinylpyrrolidinone, gelatin, hydroxycellulose, acacia, polyethylene glycol, mannitol, sodium chloride, sodium citrate or any other excipient known to one of skill in the art to pharmaceutical compositions including compounds of this
20 invention. Alternatively, the pharmaceutical compounds may be encapsulated, tableted or prepared in an emulsion or syrup for oral administration. Pharmaceutically acceptable solid or liquid carriers may be added to enhance or stabilize the composition, or to facilitate preparation of the composition. Liquid carriers include syrup, peanut oil, olive oil, glycerin,

WO 01/40243

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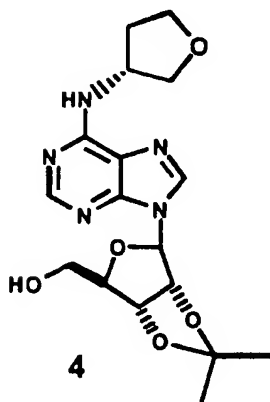
saline, alcohols and water. Solid carriers include starch, lactose, calcium sulfate, dihydrate, teffa alba, magnesium stearate or stearic acid, talc, pectin, acacia, agar or gelatin. The carrier may also include a sustained release material such as glycerol monostearate or glycerol distearate, alone or with a wax. The amount of solid carrier varies but, preferably, will be
5 between about 20 mg to about 1 gram per dosage unit. The pharmaceutical dosages are made using conventional techniques such as milling, mixing, granulation, and compressing, when necessary, for tablet forms; or milling, mixing and filling for hard gelatin capsule forms. When a liquid carrier is used, the preparation will be in the form of a syrup, elixir, emulsion or an aqueous or non-aqueous suspension. Such a liquid formulation may be administered
10 directly or filled into a soft gelatin capsule.

The Examples which follow serve to illustrate this invention. The Examples are not intended to limit the scope of this invention, but are provided to show how to make and use the compounds of this invention.

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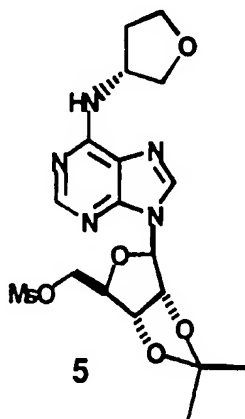
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Example 1

Intermediate – (4-{6-[(3R)oxolan-3-yl]amino}purin-9-yl)(1R, 2R, 5R)-7,7-dimethyl-3,6,8-trioxabicyclo[3.3.0]oct-2-ylmethan-1-ol (4)

5 To a solution of compound 3 (2.0 g, 6.0 mmol) and 2,2-dimethoxypropane (1.2 g, 11.8 mmol) in dimethylformamide (20 mL) was added p-toluenesulfonic acid (50 mg, 0.26 mmol) at 70°C. After 48 h at 70°C, the reaction was concentrated in vacuo to afford a solid. The solid was dissolved in methanol (3 mL), then triturated with ethyl ether (50 mL). The resultant crystals were collected by vacuum filtration to afford the intermediate 4.

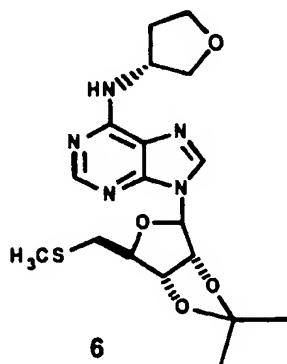


10 To a solution of 4 (190 mg, 0.5 mmol) in anhydrous pyridine (5mL), was added MsCl (80 microL, 1 mmol) at 0°C. The reaction mixture was stirred at the same temperature for 2h. Pyridine was removed under reduced pressure, residue was taken in dichloromethane (50mL), washed with water (3 x 20mL) and dried (Na₂SO₄). Evaporation of the solvent gave product 5

WO 01/40243

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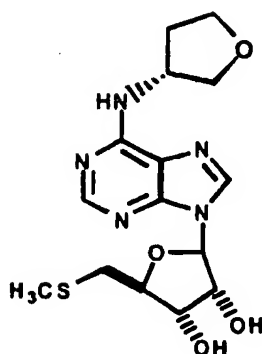
as a white foam: ^1H NMR (CDCl_3) δ 1.4 (s, 3H), 1.6 (s, 3H), 2.0-2.2 (m, 1H), 2.3-2.5 (m, 1H), 2.9 (s, 3H), 3.7-4.2 (m, 4H), 4.4-4.6 (m, 3H), 4.8-5.0 (bs, 1H), 5.1-5.2 (bs, 1H), 5.4-5.5 (bs, 1H), 6.1 (s, 1H), 6.4-6.6 (bs, 1H), 8.1 (s, 1H), 8.4 (s, 1H)



- 5 A mixture of mesylate 5 (150 mg) and methanethiolate (150mg) in acetonitrile (2mL) and water (1mL) was heated at 70 C for 24h. The solvent was evaporated under reduced pressure and the residue was purified by preparative TLC [methanol-dichloromethane (1:19)] to afford product 6: ^1H NMR (CDCl_3) δ 1.35 (s, 3H), 1.60 (s, 3H), 1.90-2.05 (m, 1H), 2.05 (s, 3H), 2.30-2.40 (m, 1H), 2.70 (doublet of AB quartet, 2H), 3.75-3.90 (m, 2H), 3.95-4.00 (m, 2H),
10 4.3-4.4 (m, 1H), 4.8-4.95 (m, 1H), 5.00-5.05 (m, 1H), 5.45-5.50 (d, 1H), 6.00-6.10 (m, 2H), 7.85 (s, 1H), 8.3 (s, 1H).

WO 01/40243

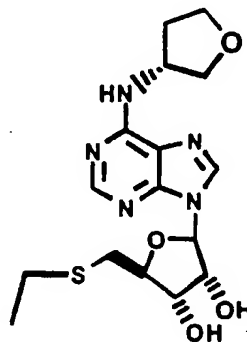
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7

2-{6-[(3R)oxolan-3-yl]amino}purin-9-yl-(4S,5S,2R,3R)-5-(methylthiomethyl)oxolane-3,4-diol (7)

Compound 6 (50mg) was dissolved in a mixture of acetic acid (8 mL) and water (2 mL) and heated at 90°C for 16 h. Solvents were removed under reduced pressure, and the residue was purified by preparative TLC [methanol-dichloromethane (1:9)] to afford compound 7: ¹H NMR (CDCl₃) δ 1.90-2.05 (m, 1H), 2.15 (s, 3H), 2.30-2.40 (m, 1H), 2.75-2.85 (m, 2H), 3.80-3.90 (m, 2H), 3.90-4.00 (m, 2H), 4.30-4.45 (m, 2H), 4.50-4.55 (m, 1H), 4.75-4.95 (m, 1H), 5.90-5.95 (m, 1H), 6.30-6.60 (m, 1H), 7.95 (s, 1H), 8.25 (s, 1H).



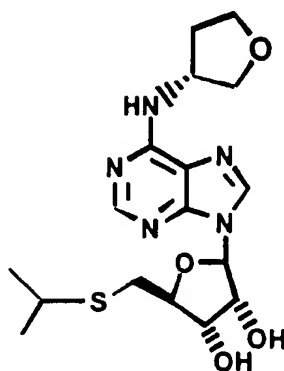
8

2-{6-[(3R)oxolan-3-yl]amino}purin-9-yl-(4S,5S,2R,3R)-5-[(Ethylthio)methyl]oxolane-3,4-diol(8)

WO 01/40243

PCT/US00/42509

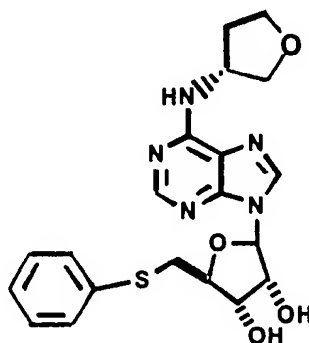
Compound 8 was prepared in the manner similar to that of 7 substituting ethane thiolate for methane thiolate. (M+1) = 382.30



10

5 2-{6-[(3R)oxolan-3-yl]amino}purin-9-yl-(4S,5S,2R,3R)-5-[(Methylethylthio)methyl]oxolane-3,4-diol(10)

Compound 10 was prepared in the manner similar to that of 7 substituting i-propane thiolate for methane thiolate. ¹H NMR (CDCl₃) δ 1.25 (d, 6H), 1.90-2.05 (m, 1H), 2.15 (s, 3H), 2.30-2.40 (m, 1H), 2.85-2.87 (d, 2H), 2.95 (septet, 1H), 3.80-3.90 (m, 2H), 3.95-4.05 (m, 2H), 4.35-4.40 (m, 2H), 4.50-4.55 (m, 1H), 4.75-4.85 (m, 1H), 5.90-5.95 (d, 1H), 6.85-6.95 (m, 1H), 7.95 (s, 1H), 8.25 (s, 1H).



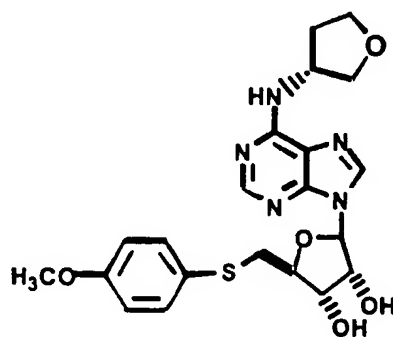
11

2-{6-[(3R)oxolan-3-yl]amino}purin-9-yl-(4S,5S,2R,3R)-5-(phenylthiomethyl)oxolane-3,4-diol(11)

WO 01/40243

PCT/US00/42509

Compound 11 was prepared in the manner similar to that of 7 substituting phenyl thiolate for methane thiolate. ¹H NMR (CDCl₃) 1.95-2.05 (m, 1H), 2.30-2.40 (m, 1H), 3.2 (d, 2H), 3.80-3.90 (m, 2H), 3.95-4.10 (m, 2H), 4.35-4.40 (d, 1H), 4.45 (t, 1H), 4.50-4.55 (m, 1H), 4.80-4.90 (m, 1H), 5.85 (d, 1H), 6.70-6.80 (m, 1H), 7.15-7.30 (m, 3H), 7.35 (d, 2H), 7.75 (s, 1H), 8.25 (s, 1H).

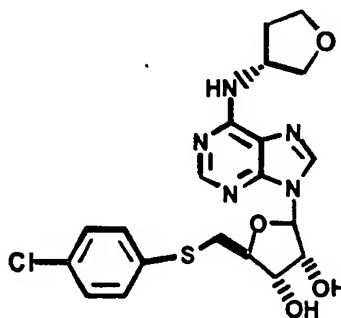


12

2-{6-(((3R)oxolan-3-yl)amino)purin-9-yl}(4S,5S,2R,3R)-5-[(4-Methoxyphenylthio)methyl]oxolane-3,4-diol(12)

This compound was prepared in the manner similar to that of 7 substituting 4-methoxyphenyl thiolate for methane thiolate.

(M+1) = 460.4



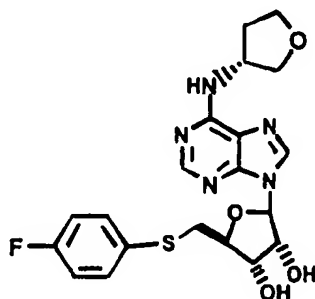
13

WO 01/40243

PCT/US00/42509

2-{6-[(3R)oxolan-3-yl]amino}purin-9-yl}(4S,5S,2R,3R)-5-[(4-chlorophenylthio)methyl]oxolane-3,4-diol(13)

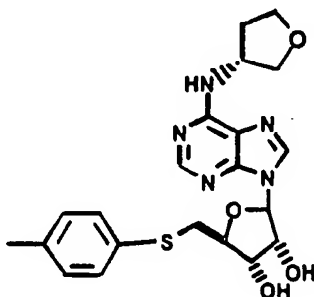
This compound was prepared in a manner similar to that of 7 substituting 4-chlorophenyl thiolate for methane thiolate. (M+1) = 464.3

**14**

5 **2-{6-[(3R)oxolan-3-yl]amino}purin-9-yl}(4S,5S,2R,3R)-5-[(4-fluorophenylthio)methyl]oxolane-3,4-diol(14)**

This compound was prepared in a manner similar to that of 7 substituting 4-fluorophenyl thiolate for methane thiolate.

(M+1) = 448.3

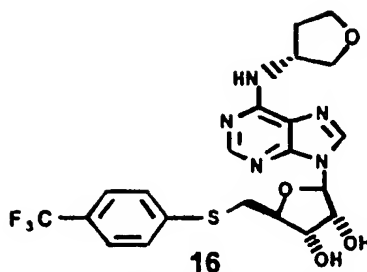
**15**

10 **2-{6-[(3R)oxolan-3-yl]amino}purin-9-yl}(4S,5S,2R,3R)-5-[(4-methylphenylthio)methyl]oxolane-3,4-diol(15)**

This compound was prepared in a manner similar to that of 7 substituting 4-methylphenyl thiolate for methane thiolate. (M+1) = 444.38

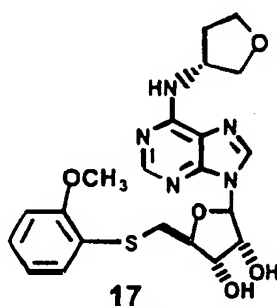
WO 01/40243

PCT/US00/42509



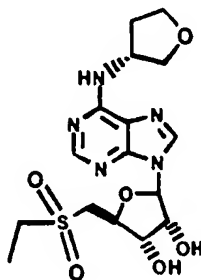
2-{6-[[[(3R)oxolan-3-yl]amino]purin-9-yl](4S,5S,2R,3R)-5-[(4-(trifluoromethyl)phenylthio)methyl]oxolane-3,4-diol(16)

This compound was prepared in a manner similar to that of 7 substituting 4-trifluoromethylphenyl thiolate for methane thiolate. (M+1) = 488.36



2-{6-[[[(3R)oxolan-3-yl]amino]purin-9-yl](4S,5S,2R,3R)-5-[(2-Methoxyphenylthio)methyl]oxolane-3,4-diol(17)

This compound was prepared in a manner similar to that of 7 substituting 2-methoxyphenyl thiolate for methane thiolate. (M+1) = 460.4



(5-{6-[[[(3R)oxolan-3-yl]amino]purinyl-9-yl](2S,3S,4R,5R)-3,4-dihydroxyoxolan-2-yl}(ethylsulfonyl)methane(9)

To a cooled solution of sulfide 8 in methanol at 0°C under nitrogen was added 3 eq. of Oxone (Potassium peroxy monosulfate) and the reaction mixture was allowed to stir at the same temperature for 1 hour. After the starting material consumed (by TLC), the reaction mixture

WO 01/40243

PCT/US00/42509

was concentrated and filtered through a small plug of silica gel. Purification by preparative TLC [methanol-dichloromethane (1:19)] afforded 9 as an off-white hygroscopic solid.

(M+1) = 414.28

5

WO 01/40243

PCT/US00/42509

EXAMPLE 2**Binding Assays – DDT₁ Cells****Cell Culture**

DDT cells (hamster vas deferens smooth muscle cell line) were grown as monolayers in petri dishes using Dulbecco's Modified Eagle's Medium (DMEM) containing 2.5 g ml⁻¹ amphotericin B, 100 U ml⁻¹ penicillin G, 0.1 mg ml⁻¹ streptomycin sulfate and 5% fetal bovine serum in a humidified atmosphere of 95% air and 5% CO₂. Cells were subcultured twice weekly by dispersion in Hank's Balanced Salt Solution (HBSS) without the divalent cations and containing 1 mM EDTA. The cells were then seeded in growth medium at a density of 1.2 x 10⁵ cells per plate and experiments were performed 4 days later at approximately one day preconfluence.

Membrane Preparations

Attached cells were washed twice with HBSS (2 x 10 ml), scraped free of the plate with the aid of a rubber policeman in 5 ml of 50 mM Tris-HCl buffer pH 7.4 at 4 °C and the suspension homogenized for 10 s. The suspension was then centrifuged at 27,000 x g for 10 min. The pellet was resuspended in homogenization buffer by vortexing and centrifuged as described above. The final pellet was resuspended in 1 vol of 50 mM Tris-HCl buffer pH 7.4 containing 5 mM MgCl₂ for A₁ AdoR assays. For the [³⁵S]GTPγS binding assay the final pellet was resuspended in 50 mM Tris-HCl pH 7.4 containing 5 mM MgCl₂, 100 mM NaCl and 1 mM dithiothreitol. This membrane suspension was then placed in liquid nitrogen for 10 min, thawed and used for assays. The protein content was determined with a Bradford™ Assay Kit using bovine serum albumin as standard.

Competitive Binding Assay

Pig striatum were prepared by homogenation in 50 mM Tris buffer (5x volume of tissue mass pH = 7.4). After centrifugation at 19,000 rpm for 25 minutes at 4 °C, the supernatant was discarded, and the process was repeated twice. Compositions of this invention were assayed to determine their affinity for the A₁ receptor in a pig striatum membrane prep or a DDT₁ membrane prep. Briefly, 0.2 mg of pig striatal membranes or DDT₁ cell membranes were treated with adenosine deaminase and 50 mM Tris buffer (pH = 7.4) followed by mixing. To the pig membranes was added 2 μL of serially diluted DMSO stock solution of the compounds of this invention at concentrations ranging from 100 microM

WO 01/40243

PCT/US00/42509

to 10 nM. The control received 2 microL of DMSO alone, then the antagonist [³H] 8-cyclopentylxanthine (CPX) for pig striatum or the agonist [³H] 2-chloro-6-cyclopentyladenosine (CCPA) for DDT₁ membranes in Tris buffer (50 mM, pH of 7.4) was added to achieve a final concentration of 2 nM. After incubation at 23 C for 2h, then the solutions were filtered using a membrane harvester using multiple washing of the membranes (3 x). The filter disks were counted in scintillation cocktail affording the amount of displacement of tritiated CPX or by the competitive binding compositions of this invention. Greater than a 5 point curve was used to generate Ki's and the number of experiments is indicated in the column marked in Table 1, below:

10

Table 1

Compound #	K _i – DDT ₁ cell membrane	K _i – Pig Striatum
7	--	222 nM
10	--	188 nM
11	--	44 nM
12	820 nM	--
14	363 nM	--
15	922 nM	--
16	7701 nM	--
17	947 nM	--

WO 01/40243

PCT/US00/42509

EXAMPLE 3**[³⁵S]GTPγS Binding Assays**

A₁-agonist stimulated [³⁵S] GTPγS binding was determined by a modification of the method described by Gierschik et al. (1991) and Lorenzen et al. (1993). Membrane protein (30-50 μg) was incubated in a volume of 0.1 ml containing 50 mM Tris-HCl buffer pH 7.4, 5 mM MgCl₂, 100 mM NaCl, 1 mM dithiothreitol, 0.2 units ml⁻¹ adenosine deaminase, 0.5% BSA, 1 mM EDTA, 10 mM GDP, 0.3 nM [³⁵S]GTPγS and with or without varying concentrations of CPA for 90 min at 30 °C. Nonspecific binding was determined by the addition of 10 μM GTPγS. Agonist stimulated binding was determined as the difference between total binding in the presence of CPA and basal binding determined in the absence of CPA. Previous reports have shown that agonist stimulated [³⁵S]GTPγS binding was dependent on the presence of GDP (Gierschik et al., 1991; Lorenzen et al., 1993; Traynor & Nahorski, 1995). In preliminary experiments, it was found that 10 μM GDP gave the optimal stimulation of CPA dependent [³⁵S]GTPγS binding and this concentration was therefore used in all studies. In saturation experiments, 0.5 nM [³⁵S]GTPγS was incubated with 0.5-1000 nM GTPγS. At the end of the incubation, each suspension was filtered and the retained radioactivity determined as described above. Results are presented normalized to the full agonist N-6-cyclopentyladenosine, CPA.

Table 2

Compound #	GTPS
CPA	100 %
8	104%
12	52%
13	69%
14	61%
15	48%
16	31%
17	52%

20

WO 01/40243

PCT/US00/42509

EXAMPLE 4**cAMP Assay**

A scintillation proximity assay (SPA) using rabbit antibodies directed at cAMP using an added tracer of adenosine 3',5'-cyclic phosphoric acid 2'-O-succinyl-3-[¹²⁵I]iodotyrosine methyl ester and fluoromicrospheres containing anti-rabbit specific antibodies as described by Amersham Pharmacia Biotech (Biotrak cellular communication assays). Briefly, DDT₁ cells were cultured in clear bottomed 96 well microtiter plates with opaque wells at concentrations between 10⁴ to 10⁶ cells per well in 40 µl of HBSS at 37 °C (5% CO₂ and 95% humidity). The partial or full A₁ agonists (5 µl) of this invention were incubated at various concentrations with the DDT₁ cells in the presence of rolipram (50 µM), and 5 µM forskolin for 10 min at 37 °C. The cells were immediately lysed by treatment 5 µl of 10% dodecyltrimethylammonium bromide followed by shaking using microplate shaker. After incubation of the plate for 5 minutes, an immunoreagent solution (150 µl containing equal volumes of tracer, antiserum, and SPA fluorospheres) was added to each well followed by sealing the plate. After 15-20 h at 23 °C, the amount of bound [¹²⁵I] cAMP to the fluoromicrospheres was determined by counting in a microtitre plate scintillation counter for 2 minutes. Comparison of counts with standard curves generated for cAMP using a similar protocol afforded the cAMP present after cell lysis. Results are presented normalized to the full agonist N-6-cyclopentyladenosine, CPA. Thus, the full agonist CPA diminished the amount of forskolin induced cAMP generation back to basal levels.

Table 3

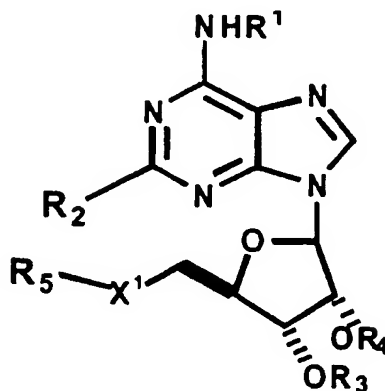
Compound #	cAMP
CPA	107 %
8	37%
12	-9%
13	30%
14	47%
15	22%
16	22%
17	18%

WO 01/40243

PCT/US00/42509

What we claim is:

1. A composition of matter having the formula:



5 wherein $X^1 = S, S(O), S(O)_2$;

R^1 is a monocyclic or polycyclic heterocyclic group containing from 3 to 15 carbon atoms wherein at least one carbon atom is substituted with an atom or molecule selected from the group consisting of N, O, P and $S-(O)_{0,2}$ wherein R^1 does not contain an epoxide group;

R_2 is selected from the group consisting of hydrogen, halo, CF_3 , and cyano;

10 R_3 and R_4 are each independently selected from the group consisting of hydrogen, $-(CO)-R'$, and $-(CO)-R''$ wherein R' and R'' are each independently selected from the group consisting of C_{1-15} alkyl, C_{2-15} alkenyl, C_{2-15} alkynyl, heterocyclyl, aryl, and heteroaryl, which alkyl, alkenyl, alkynyl, aryl, heterocyclyl, and heteroaryl are optionally substituted with from 1 to 3 substituents independently selected from the group of halo, NO_2 , heterocyclyl, aryl, heteroaryl, CF_3 , CN, OR^{20} , SR^{20} , $S(O)R^{22}$, SO_2R^{22} , $SO_2N(R^{20})_2$, $SO_2NR^{20}COR^{22}$, $SO_2NR^{20}CO_2R^{22}$, $SO_2NR^{20}CON(R^{20})_2$, $N(R^{20})_2$, $NR^{20}COR^{22}$, $NR^{20}CO_2R^{22}$, $NR^{20}CON(R^{20})_2$, $NR^{20}C(NR^{20})NHR^{21}$, COR^{20} , CO_2R^{20} , $CON(R^{20})_2$, $CONR^{20}SO_2R^{22}$, $NR^{20}SO_2R^{22}$, $SO_2NR^{20}CO_2R^{22}$, $OCONR^{20}SO_2R^{22}$, $OC(O)R^{20}$, $C(O)OCH_2OC(O)R^{20}$, and $OCON(R^{20})_2$ and
15 wherein each optional heteroaryl, aryl, and heterocyclyl substituent is further optionally substituted with halo, NO_2 , alkyl, CF_3 , amino, mono- or di- alkylamino, alkyl or aryl or heteroaryl amide, $NR^{20}COR^{22}$, $NR^{20}SO_2R^{22}$, COR^{20} , CO_2R^{20} , $CON(R^{20})_2$, $NR^{20}CON(R^{20})_2$, $OC(O)R^{20}$, $OC(O)N(R^{20})_2$, SR^{20} , $S(O)R^{22}$, SO_2R^{22} , $SO_2N(R^{20})_2$, CN, or OR^{20} ;
20

WO 01/40243

PCT/US00/42509

R_3 is selected from the group consisting of C_{1-15} alkyl, C_{2-15} alkenyl, C_{2-15} alkynyl, heterocyclyl, aryl, and heteroaryl, wherein each alkyl, alkenyl, alkynyl, aryl, heterocyclyl, and heteroaryl are optionally substituted with from 1 to 3 substituents independently selected from the group consisting of halo, alkyl, NO_2 , heterocyclyl, aryl, heteroaryl, CF_3 , CN, OR^{20} , SR^{20} , $S(O)_2R^{20}$, $S(O)R^{22}$, SO_2R^{22} , $SO_2N(R^{20})_2$, $SO_2NR^{20}COR^{22}$, $SO_2NR^{20}CO_2R^{22}$, $SO_2NR^{20}CON(R^{20})_2$, $P(O)(OR^{20})_2$, $N(R^{20})_2$, $NR^{20}COR^{22}$, $NR^{20}CO_2R^{22}$, $NR^{20}CON(R^{20})_2$, $NR^{20}C(NR^{20})NHR^{23}$, COR^{20} , CO_2R^{20} , $CON(R^{20})_2$, $CONR^{20}SO_2R^{22}$, $NR^{20}SO_2R^{22}$, $SO_2NR^{20}CO_2R^{22}$, $OCONR^{20}SO_2R^{22}$, $OC(O)R^{20}$, $C(O)OCH_2OC(O)R^{20}$, and $OCON(R^{20})_2$ and wherein the optional heteroaryl, aryl, and heterocyclyl substituent are each further optionally substituted with halo, NO_2 , alkyl, CF_3 , amino, mono- or di-alkylamino, alkyl or aryl or heteroaryl amide, $NR^{20}COR^{22}$, $NR^{20}SO_2R^{22}$, COR^{20} , CO_2R^{20} , $CON(R^{20})_2$, $NR^{20}CON(R^{20})_2$, $OC(O)R^{20}$, $OC(O)N(R^{20})_2$, SR^{20} , $S(O)R^{22}$, SO_2R^{22} , $SO_2N(R^{20})_2$, CN, or OR^{20} ;

R^{20} is selected from the group consisting of H, C_{1-15} alkyl, C_{2-15} alkenyl, C_{2-15} alkynyl, heterocyclyl, aryl, and heteroaryl, which alkyl, alkenyl, alkynyl, heterocyclyl, aryl, and heteroaryl are optionally substituted with from 1 to 3 substituents independently selected from halo, alkyl, mono- or dialkylamino, alkyl or aryl or heteroaryl amide, CN, $O-C_{1-6}$ alkyl, CF_3 , aryl, and heteroaryl; and

R^{22} is selected from the group consisting of C_{1-15} alkyl, C_{2-15} alkenyl, C_{2-15} alkynyl, heterocyclyl, aryl, and heteroaryl, which alkyl, alkenyl, alkynyl, heterocyclyl, aryl, and heteroaryl are optionally substituted with from 1 to 3 substituents independently selected from halo, alkyl, mono- or dialkylamino, alkyl or aryl or heteroaryl amide, CN, $O-C_{1-6}$ alkyl, CF_3 , and heteroaryl.

2. The composition of claim 1 wherein R_3 is selected from the group consisting of hydrogen, and halo;

R_3 and R_4 are each independently selected from the group consisting of hydrogen, $-(CO)-R'$, and $-(CO)-R''$ wherein R' and R'' are each independently selected from the group consisting of C_{1-15} alkyl, heterocyclyl, aryl, and heteroaryl, which alkyl, aryl, heterocyclyl, and heteroaryl are each optionally substituted with from 1 to 2 substituents independently selected from the group of halo, NO_2 , heterocyclyl, aryl, heteroaryl, CF_3 , CN, OR^{20} , $S(O)R^{22}$, SO_2R^{22} , $SO_2N(R^{20})_2$, $N(R^{20})_2$, $NR^{20}COR^{22}$, $NR^{20}CO_2R^{22}$, $NR^{20}CON(R^{20})_2$, $NR^{20}C(NR^{20})NHR^{23}$, COR^{20} , CO_2R^{20} , $CON(R^{20})_2$, $CONR^{20}SO_2R^{22}$, $NR^{20}SO_2R^{22}$ and wherein each optional heteroaryl, aryl,

WO 01/40243

PCT/US00/42509

and heterocyclyl substituent is further optionally substituted with halo, NO₂, alkyl, CF₃, amino, mono- or di- alkylamino, CN, or OR²⁰;

R₃ is selected from the group consisting of C₁₋₁₅ alkyl, C₂₋₁₅ alkenyl, C₂₋₁₅ alkynyl, heterocyclyl, aryl, and heteroaryl, wherein alkyl, alkenyl, alkynyl, aryl, heterocyclyl, and heteroaryl are optionally substituted with from 1 to 3 substituents independently selected from the group of halo, alkyl, heterocyclyl, aryl, heteroaryl, CF₃, CN, OR²⁰, SR²⁰, N(R²⁰)₂, S(O)R²², S(O)₂R²⁰, SO₂R²², SO₂N(R²⁰)₂, NR²⁰CO₂R²², NR²⁰CON(R²⁰)₂, COR²⁰, CO₂R²⁰, CON(R²⁰)₂, and wherein each optional heteroaryl, and aryl substituent is optionally substituted with halo, alkyl, CF₃, CO₂R²⁰, CON(R²⁰)₂, NR²⁰CON(R²⁰)₂, SR²⁰, S(O)R²², SO₂R²², SO₂N(R²⁰)₂, CN, or OR²⁰;

R²⁰ is selected from the group consisting of H, C₁₋₁₅ alkyl, aryl, and heteroaryl, which alkyl, aryl, and heteroaryl are each optionally substituted with from 1 to 2 substituents independently selected from halo, alkyl, mono- or dialkylamino, CN, O-C₁₋₆ alkyl, CF₃; and

R²² is selected from the group consisting of C₁₋₁₅ alkyl, aryl, and heteroaryl, which alkyl, aryl, and heteroaryl are each optionally substituted with from 1 to 2 substituents independently selected from halo, alkyl, mono- or dialkylamino, alkyl or CN, O-C₁₋₆ alkyl, and CF₃.

3. The composition of claim 1 wherein R₃ is a hydrogen;

R₃ and R₄ are each independently selected from the group consisting of hydrogen, –(CO)-R' and –(CO)-R'' wherein R' and R'' are each independently selected from the group consisting of C₁₋₁₀ alkyl, aryl, and heteroaryl, which alkyl, aryl, and heteroaryl are optionally substituted with from 1 to 2 substituents independently selected from the group of halo, NO₂, aryl, heteroaryl, CF₃, CN, OR²⁰, N(R²⁰)₂, S(O)R²², SO₂R²², NR²⁰COR²², COR²⁰, CO₂R²⁰, CON(R²⁰)₂, NR²⁰SO₂R²², and wherein each optional heteroaryl, aryl, and heterocyclyl substituent is further optionally substituted with halo, NO₂, alkyl, CF₃;

R₅ is selected from the group consisting of C₁₋₁₅ alkyl, C₂₋₁₅ alkenyl, heterocyclyl, aryl, and heteroaryl, wherein each alkyl, alkenyl, aryl, heterocyclyl, and heteroaryl are optionally substituted with from 1 to 3 substituents independently selected from the group consisting of halo, alkyl, aryl, heteroaryl, CF₃, CN, OR²⁰, SR²⁰, N(R²⁰)₂, S(O)R²², SO₂R²², SO₂N(R²⁰)₂, NR²⁰CO₂R²², NR²⁰CON(R²⁰)₂, COR²⁰, CO₂R²⁰, CON(R²⁰)₂, and wherein each optional heteroaryl, and aryl substituent is further optionally substituted with halo, alkyl, CF₃, CO₂R²⁰,

WO 01/40243

PCT/US00/42509

CON(R²⁰)₂, NR²⁰CON(R²⁰)₂, S(O)R²², SO₂R²², SO₂N(R²⁰)₂, CN, and OR²⁰;

R²⁰ is selected from the group consisting of H, C₁₋₆ alkyl, and aryl, which alkyl, and aryl, are optionally substituted with 1 substituent selected from halo, alkyl, mono- or dialkylamino, CN, O-C₁₋₆ alkyl, CF₃; and

5 R²² is selected from the group consisting of C₁₋₆ alkyl and aryl, which alkyl and aryl are optionally substituted with 1 substituent independently selected from halo, alkyl, mono- or dialkylamino, alkyl or CN, O-C₁₋₆ alkyl, and CF₃.

4. The composition of claim 1 wherein R₂ is a hydrogen;

R₃ and R₄ are each independently selected from the group consisting of hydrogen, -
10 (CO)-R' and -(CO)-R'' wherein R' and R'' are each independently selected from the group consisting of C₁₋₆ alkyl, and aryl, which alkyl and aryl are optionally substituted with from 1 to 2 substituents independently selected from the group of halo, NO₂, aryl, CF₃, CN, OR²⁰, N(R²⁰)₂, S(O)R²², SO₂R²², N(R²⁰)₂, and wherein each optional aryl substituent is optionally substituted with halo, NO₂, alkyl, CF₃;

15 R₅ is selected from the group consisting of C₁₋₁₅ alkyl, C₂₋₁₅ alkenyl, aryl, and heteroaryl, wherein alkyl, alkenyl, aryl, and heteroaryl are optionally substituted with from 1 to 3 substituents independently selected from the group consisting of halo, alkyl, aryl, heteroaryl, CF₃, CN, OR²⁰, SR²⁰, N(R²⁰)₂, S(O)R²², SO₂R²², SO₂N(R²⁰)₂, NR²⁰CO₂R²², NR²⁰CON(R²⁰)₂, CO₂R²⁰, CON(R²⁰)₂, and wherein each optional heteroaryl, and aryl
20 substituent is further optionally substituted with halo, alkyl, CF₃, CO₂R²⁰, CON(R²⁰)₂, S(O)R²², SO₂R²², SO₂N(R²⁰)₂, CN, or OR²⁰;

R²⁰ is selected from the group consisting of H, C₁₋₆ alkyl, and aryl, which alkyl and aryl are optionally substituted with 1 substituent selected from halo, alkyl, mono- or dialkylamino, CN, O-C₁₋₆ alkyl, CF₃; and

25 R²² is selected from the group consisting of C₁₋₆ alkyl and aryl, which alkyl and aryl are optionally substituted with 1 substituent selected from halo, alkyl or CN, O-C₁₋₆ alkyl, and CF₃.

5. The composition of claim 1 wherein R₂ is a hydrogen;

R₃ and R₄ are each independently selected from the group consisting of hydrogen, -
30 (CO)-R' and -(CO)-R'' wherein each R' and R'' are independently selected from the group consisting of C₁₋₆ alkyl which alkyl are optionally substituted with 1 substituent selected from

WO 01/40243

PCT/US00/42509

the group of aryl, CF_3 , CN, OR^{20} , $\text{N}(\text{R}^{20})_2$, and wherein each optional aryl substituent is further optionally substituted with halo, NO_2 , alkyl, CF_3 ;

R_5 is selected from the group consisting of C_{1-8} alkyl, C_{2-8} alkenyl, and aryl wherein alkyl, alkenyl, and aryl are optionally substituted with from 1 to 2 substituents independently
5 selected from the group consisting of halo, alkyl, aryl, heteroaryl, CF_3 , CN, OR^{22} , $\text{S}(\text{O})\text{R}^{22}$, SO_2R^{22} , $\text{SO}_2\text{N}(\text{R}^{20})_2$, $\text{NR}^{20}\text{CON}(\text{R}^{20})_2$, CO_2R^{20} , $\text{CON}(\text{R}^{20})_2$, and wherein each optional heteroaryl, and aryl substituent is further optionally substituted with halo, alkyl, CF_3 , CO_2R^{20} , CN, and OR^{20} ;

R^{20} is selected from the group consisting of H, C_{1-6} alkyl; and

10 R^{22} is selected from the group consisting of C_{1-6} .

6. The composition of claim 1 wherein $\text{X}^1=\text{S}$ or SO_2 ;

R_2 is a hydrogen;

R_3 and R_4 are each independently selected from the group consisting of hydrogen, $-(\text{CO})-\text{R}'$ and $-(\text{CO})-\text{R}''$ wherein R' and R'' are each independently selected from the group
15 consisting of C_{1-6} alkyl;

R_5 is selected from the group consisting of C_{1-8} alkyl, and aryl wherein alkyl, and aryl are optionally substituted with from 1 to 2 substituents independently selected from the group consisting of halo, alkyl, aryl, heteroaryl, CF_3 , CN, OR^{20} , $\text{S}(\text{O})\text{R}^{22}$, SO_2R^{22} , $\text{SO}_2\text{N}(\text{R}^{20})_2$,
20 $\text{NR}^{20}\text{CON}(\text{R}^{20})_2$, CO_2R^{20} , $\text{CON}(\text{R}^{20})_2$, and wherein each optional heteroaryl, and aryl substituent is further optionally substituted with halo, alkyl, CF_3 , CO_2R^{20} , CN, and OR^{20} ;

R^{20} is selected from the group consisting of H, C_{1-6} alkyl; and

R^{22} is selected from the group consisting of C_{1-6} .

7. The composition of claim 1 wherein $\text{X}^1=\text{S}$ or SO_2 ;

R_2 is a hydrogen;

25 R_3 and R_4 are hydrogen;

R_5 is selected from the group consisting of C_{1-8} alkyl, and aryl wherein alkyl, and aryl are optionally substituted with from 1 to 2 substituents independently selected from the group consisting of halo, alkyl, CF_3 , CN, OR^{20} , CO_2R^{20} ; and

R^{20} is selected from the group consisting of H, C_{1-6} alkyl.

30 8. The composition of claim 1 wherein $\text{X}^1=\text{S}$ or SO_2 ;

R_2 is a hydrogen;

WO 01/40243

PCT/US00/42509

R_3 and R_4 are hydrogen;

R_5 is selected from the group consisting of C_{1-8} alkyl, and aryl wherein alkyl, and aryl are optionally substituted with from 1 to 2 substituents independently selected from the group consisting of halo, alkyl, CF_3 , OR^{20} ; and

5 R^{20} is selected from the group consisting of H, C_{1-6} alkyl.

9. The composition of claim 1 wherein $X^1=S$ or SO_2 ;

R_2 is a hydrogen;

R_3 and R^4 are independently selected from the group consisting of hydrogen, $-(CO)-R'$ and $-(CO)-R''$ wherein R' and R'' are each independently selected from the group consisting of C_{1-6} alkyl which alkyl are optionally substituted with 1 substituent selected from the group consisting of aryl, CF_3 , CN, OR^{20} , $N(R^{20})_2$, and wherein each optional aryl substituent is further optionally substituted with halo, NO_2 , alkyl, CF_3 ;

R_5 is C_{1-8} alkyl, wherein alkyl, is optionally substituted with from 1 to 2 substituents independently selected from the group consisting of halo, alkyl, aryl, heteroaryl, CF_3 , CN, OR^{20} , $S(O)R^{22}$, SO_2R^{22} , $SO_2N(R^{20})_2$, $NR^{20}CON(R^{20})_2$, CO_2R^{20} , $CON(R^{20})_2$, wherein each optional heteroaryl, and aryl substituent is further optionally substituted with halo, alkyl, CF_3 , CO_2R^{20} , CN, and OR^{20} ;

R^{20} is selected from the group consisting of H, C_{1-6} alkyl; and

R^{22} is selected from the group consisting of C_{1-6} .

20 10. The composition of claim 1 wherein $X^1=S$ or SO_2 ;

R_2 is a hydrogen;

R_3 and R_4 are independently selected from the group consisting of hydrogen, $-(CO)-R'$ and $-(CO)-R''$ wherein R' and R'' are each independently selected from the group consisting of C_{1-6} alkyl;

25 R_5 is C_{1-8} alkyl that is optionally substituted with from 1 to 2 substituents independently selected from the group consisting of aryl, heteroaryl, OR^{20} , $S(O)R^{22}$, CO_2R^{20} , $CON(R^{20})_2$, and wherein each optional heteroaryl, and aryl substituent is further optionally substituted with halo, alkyl, CF_3 , CO_2R^{20} , CN, and OR^{20} ;

R^{20} is selected from the group consisting of H, C_{1-3} alkyl; and

30 R^{22} is selected from the group consisting of C_{1-6} .

11. The composition of claim 1 wherein $=S$ or SO_2 ;

WO 01/40243

PCT/US00/42509

R_2 is a hydrogen;

R_3 and R_4 are hydrogen;

R_5 is C_{1-8} alkyl that is optionally substituted with 1 substituent selected from the group consisting of CO_2R^{20} , and $CON(R^{20})_2$; and

5 R^{20} is selected from the group consisting of H, and methyl.

12. The composition of claim 11 wherein R_5 is C_{1-6} alkyl.

13. The composition of claim 11 wherein R_5 is selected from the group consisting of methyl and ethyl and isopropyl.

14. The composition of claim 1 wherein R_2 is a hydrogen;

10 R_3 and R_4 are each independently selected from the group consisting of hydrogen, $-(CO)-R'$ and $-(CO)-R''$ wherein each R' and R'' are independently selected from the group consisting of C_{1-6} alkyl, and aryl, which alkyl and aryl are optionally substituted with from 1 to 2 substituents independently selected from the group of halo, NO_2 , aryl, CF_3 , CN , OR^{20} , $N(R^{20})_2$, $S(O)R^{22}$, SO_2R^{22} , $N(R^{20})_2$, and wherein each optional aryl substituent is further
15 optionally substituted with halo, NO_2 , alkyl, CF_3 ;

R_5 is selected from the group consisting of, aryl, and heteroaryl, wherein aryl, and heteroaryl are optionally substituted with from 1 to 3 substituents independently selected from the group consisting of halo, alkyl, aryl, heteroaryl, CF_3 , CN , OR^{20} , SR^{20} , $N(R^{20})_2$, $S(O)R^{22}$, SO_2R^{22} , $SO_2N(R^{20})_2$, $NR^{20}CO_2R^{22}$, $NR^{20}CON(R^{20})_2$, CO_2R^{20} , $CON(R^{20})_2$, and wherein each
20 optional heteroaryl, and aryl substituent is further optionally substituted with halo, alkyl, CF_3 , CO_2R^{20} , $CON(R^{20})_2$, $S(O)R^{22}$, SO_2R^{22} , $SO_2N(R^{20})_2$, CN , or OR^{20} ;

R^{20} is selected from the group consisting of H, C_{1-6} alkyl, and aryl, which alkyl and aryl are optionally substituted with 1 substituent selected from halo, alkyl, mono- or dialkylamino, CN , $O-C_{1-6}$ alkyl, CF_3 ; and

25 R^{22} is selected from the group consisting of C_{1-6} alkyl and aryl, which alkyl and aryl are optionally substituted with 1 substituent selected from halo, alkyl or CN , $O-C_{1-6}$ alkyl, and CF_3 .

15. The composition of claim 1 wherein $X^1=S$;

R_2 is a hydrogen;

WO 01/40243

PCT/US00/42509

R_3 and R_4 are each independently selected from the group consisting of hydrogen, $-(CO)-R'$ and $-(CO)-R''$ wherein R' and R'' are each independently selected from the group consisting of C_{1-6} alkyl;

R_5 is selected from the group consisting of, aryl, and heteroaryl, wherein aryl, and heteroaryl are optionally substituted with from 1 to 3 substituents independently selected from the group consisting of halo, alkyl, CF_3 , CN, OR^{20} , SR^{20} , CO_2R^{20} , $CON(R^{20})_2$; and

R^{20} is selected from the group consisting of H, C_{1-3} alkyl.

16. The composition of claim 1 wherein $X^1=S$;

R_3 is a hydrogen;

10 R_3 and R_4 are hydrogen;

R_5 is aryl that is optionally substituted with from 1 to 2 substituents independently selected from the group consisting of halo, alkyl, CF_3 , OR^{20} , CO_2R^{20} , $CON(R^{20})_2$;

R^{20} is selected from the group consisting of H, and methyl; and

R^{22} is selected from the group consisting of C_{1-6} alkyl.

15 17. The composition of claim 16 wherein R_5 is phenyl that is optionally substituted with a substituent selected from the group consisting of methoxy, chloro, fluoro, methyl, and trifluoromethyl.

18. The composition of claim 1 wherein R^1 is mono or polysubstituted with one or more compounds selected from the group consisting of halogen, oxo, hydroxyl, lower alkyl, substituted lower alkyl, alkoxy, aryl, acyl, aryloxy, carboxyl, substituted aryl, heterocycle, heteroaryl, substituted heteroaryl, cycloalkyl, substituted cycloalkyl, nitro, cyano and mixtures thereof.

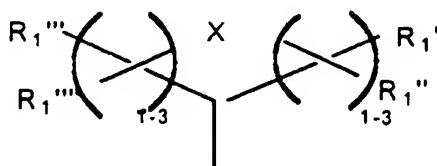
19. The composition of matter of claim 1 wherein R^1 is a monocyclic, bicyclic, or tricyclic cycloalkyl group containing from 3 to 15 carbon atoms wherein at least one carbon atom is substituted with an atom or molecule selected from the group consisting of O or S- $(O)_{0-2}$.

20. The composition of claim 19 wherein R^1 is mono or polysubstituted with one or more compounds selected from the group consisting of halogen, oxo, hydroxyl, lower alkyl, substituted lower alkyl, alkoxy, aryl, acyl, aryloxy, carboxyl, substituted aryl, heterocycle, heteroaryl, substituted heteroaryl, cycloalkyl, substituted cycloalkyl, nitro, cyano and mixtures thereof.

WO 01/40243

PCT/US00/42509

21. The composition of claim 1 wherein R¹ is:



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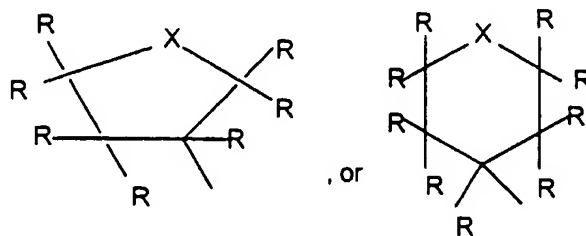
wherein R₁['], R₁^{''}, R₁^{'''}, and R₁^{''''} are each independently selected from the group halogen, hydroxyl, lower alkyl, substituted lower alkyl, alkoxy, aryl, acyl, aryloxy, carboxyl, substituted aryl, heterocycle, heteroaryl, substituted heteroaryl, cycloalkyl, substituted cycloalkyl, nitro, cyano and mixtures thereof and X is O, or S (-O)₀₋₂.

22. The composition of claim 21 wherein R₁^{'''} and R₁^{''''} can together be a single oxygen atom.

23. The composition of claim 21 wherein R₁['], R₁^{''}, R₁^{'''}, and R₁^{''''} are each individually selected from the group H, lower alkyl, substitute lower alkyl, alkoxy, aryl, and substituted aryl.

24. The composition of claim 21 wherein R₁['], R₁^{''}, R₁^{'''}, and R₁^{''''} are each individually selected from the group H, lower alkyl, and substitute lower alkyl.

25. The composition of claim 1 wherein R¹ is selected from the group consisting of:



WO 01/40243

PCT/US00/42509

wherein each R may be independently selected from the group consisting of H, lower alkyl, and substituted lower alkyl and wherein X is O, or S (-O)_n.

26. The composition of claims 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 wherein R₁ is selected from the group consisting of 3-tetrahydrofuranyl, 3-tetrahydrothiofuranyl, 4-pyranyl, and 4 thiopyranyl.

27. The composition of claims 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 wherein R₁ is 3-tetrahydrofuranyl.

28. The composition of claim 1 wherein the compound is selected from the group of compounds consisting of 2-{6-[(3R)oxolan-3-yl]amino}purin-9-yl}(4S,5S,2R,3R)-5-(methylthiomethyl)oxolane-3,4-diol; 2-{6-[(3R)oxolan-3-yl]amino}purin-9-yl}(4S,5S,2R,3R)-5-[(Ethylthio)methyl]oxolane-3,4-diol; 2-{6-[(3R)oxolan-3-yl]amino}purin-9-yl}(4S,5S,2R,3R)-5-[(Methylethylthio)methyl]oxolane-3,4-diol; 2-{6-[(3R)oxolan-3-yl]amino}purin-9-yl}(4S,5S,2R,3R)-5-(phenylthiomethyl)oxolane-3,4-diol; 2-{6-[(3R)oxolan-3-yl]amino}purin-9-yl}(4S,5S,2R,3R)-5-[(4-Methoxyphenylthio)methyl]oxolane-3,4-diol; 2-{6-[(3R)oxolan-3-yl]amino}purin-9-yl}(4S,5S,2R,3R)-5-[(4-chlorophenylthio)methyl]oxolane-3,4-diol; 2-{6-[(3R)oxolan-3-yl]amino}purin-9-yl}(4S,5S,2R,3R)-5-[(4-fluorophenylthio)methyl]oxolane-3,4-diol; 2-{6-[(3R)oxolan-3-yl]amino}purin-9-yl}(4S,5S,2R,3R)-5-[(4-methylphenylthio)methyl]oxolane-3,4-diol; 2-{6-[(3R)oxolan-3-yl]amino}purin-9-yl}(4S,5S,2R,3R)-5-[(4-trifluoromethyl)phenylthio)methyl]oxolane-3,4-diol; 2-{6-[(3R)oxolan-3-yl]amino}purin-9-yl}(4S,5S,2R,3R)-5-[(2-Methoxyphenylthio)methyl]oxolane-3,4-diol, and (5-{6-[(3R)oxolan-3-yl]amino}purin-9-yl}(2S,3S,4R,5R)-3,4-dihydroxyoxolan-2-yl)(ethylsulfonyl)methane.

29. A method for modifying cardiac activity in a mammal experiencing a heart electrical disorder that can be treated by stimulating an A₁ adenosine receptor comprising the administration of a therapeutically effective amount of the composition of claim 1 to the mammal.

30. A method for modifying mammalian adipocyte function by stimulating an A₁ adenosine receptor comprising administering a therapeutically effective amount of the composition of claim 1 to the mammal.

WO 01/40243

PCT/US00/42509

31. A method to restore sensitivity and efficacy of insulin in a mammal by stimulating an A₁ adenosine receptor comprising the administration of a therapeutically effective amount of a composition of claim 1 to the mammal.

32. A method for providing a mammal with central nervous system
5 neuroprotection by stimulating an A₁ adenosine receptor comprising administering a therapeutically effective amount of the composition of claim 1 to the mammal.

33. A method for providing a mammal with cardiomyocyte protection from ischemia by stimulating an A₁ adenosine receptor comprising administering a therapeutically effective amount of the composition of claim 1 to the mammal.

10 34. The method of claim 29 or 30 or 31 or 32 or 33 wherein the therapeutically effective amount ranges from about 0.01 to about 100 mg/kg weight of the mammal.

35. The method of claim 29 wherein the composition is administered to the mammal experiencing a heart electrical disorder selected from the group consisting of supraventricular tachycardias, atrial fibrillation, atrial flutter, and AV nodal re-entrant
15 tachycardia.

36. The method of claim 30 or 31 wherein the composition is administered to a mammal experiencing a disorder selected from the group consisting of diabetes and obesity.

37. The method of claim 32 wherein the composition is administered to a mammal experiencing an central nervous system disorder selected from the group consisting of
20 epilepsy, and stroke.

38. The method of claim 33 wherein the composition is administered to a mammal experiencing an ischemic event in the heart selected from the group consisting of stable angina, unstable angina, cardiac transplant, and myocardial infarction.

39. The method of claim 29 or 30 or 31 or 32 or 33 wherein the mammal is a human.

25 40. A pharmaceutical composition of matter comprising the composition of claim 1 and one or more pharmaceutical excipients.

41. The pharmaceutical composition of matter of claim 40 wherein the pharmaceutical composition is in the form of a solution.

42. The pharmaceutical composition of matter of claim 40 wherein the
30 pharmaceutical composition is in the form of a tablet.

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